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VOLUME 128 • NUMBER 1 **JANUARY 1978**

1 *Diagnostic Clues in Metastatic Lesions of Endocarditis in Addicts*
HARAGOPAL THADEPALLI, MD, and CHARLES K. FRANCIS, MD

6 *Splenic Subcapsular Hematoma—Ultrasonic Diagnosis*
ROBERT L. WILSON, MD; WILLIAM F. ROGERS, MD; MICHAEL S. SHAUB, MD, and LCDR WILLIAM BIRNBAUM, MC, USNR

9 *Thoracic Outlet Syndrome* WARD W. WOODS, MD

MEDICAL PROGRESS

13 *Cholesterol Metabolism in Man* SCOTT M. GRUNDY, MD, PhD

SPECIALTY CONFERENCE

26 *Paraquat Ingestion and Pulmonary Injury*
Participants: JUDITH PICKERSGILL, MD; EUGENE D. ROBIN, MD; JAMES THEODORE, MD; THOMAS A. RAFFIN, MD; PAUL DAVID LAMAN, MD, and LAWRENCE M. SIMON, MD
Pulmonary Rounds at Stanford University School of Medicine

MEDICAL STAFF CONFERENCE

35 *Hereditary Spherocytosis Revisited—Eighth Annual Paul M. Aggeler Memorial Lecture*
Guest Lecturer: WILLIAM N. VALENTINE, MD

46 *Pathology*

EDITORIALS

54 • *A Step in the Right Direction* • *Cholesterol Metabolism and Human Disease*
• *Paraquat Poisoning: An Update* • *'Do As I Say'*

CASE REPORTS

60 *Rapid Resolution of a Pulmonary Embolus in Man*
WALTER S. JAMES III, MD; STUART J. MENN, MD, and KENNETH M. MOSER, MD

64 *Anorectal Lesions and Syphilitic Hepatitis*
MAJ DAVID R. HABURCHAK, MC, USA, and CPT HOWARD DAVIDSON, MC, USA

CORRESPONDENCE

68 • *Traumatic Fibromyositis* • *Traumatic Fibromyositis or Myofascial Trigger Points?*
• *Survival in Lung Cancer* • *Outpatient Cardiac Catheterization*
• *A Monumental Squeak* • *Correction: Anastomosis*

HEALTH CARE DELIVERY

75 *Factors Influencing the Location of Rural General Practitioners—A Study in Washington State*
SAM M. CORDES, PhD

81 *Medical School Graduates Who Leave California—A Study at the University of California, San Francisco* HARRISON G. GOUGH, PhD, and WALLACE B. HALL, PhD

MEDICAL EDUCATION

85 *Unprofessional Physicians—Some Correlative Data*
G. GORDON HADLEY, MD, and JERE E. CHRISPENS, MA

MEDICAL INFORMATION

89 *Venereal Transmission of Intestinal Parasites* ALFRED L. HURWITZ, MD, and ROBERT L. OWEN, MD

92 *Articles to Read in Other Journals*

93 *Book Reviews* • *Books Received, see Advertising Page 20*

96 *In Memoriam*

98 *Proposed CMA Constitutional Amendments*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, ALASKA, MONTANA AND IDAHO**
(See Advertising Page 35)

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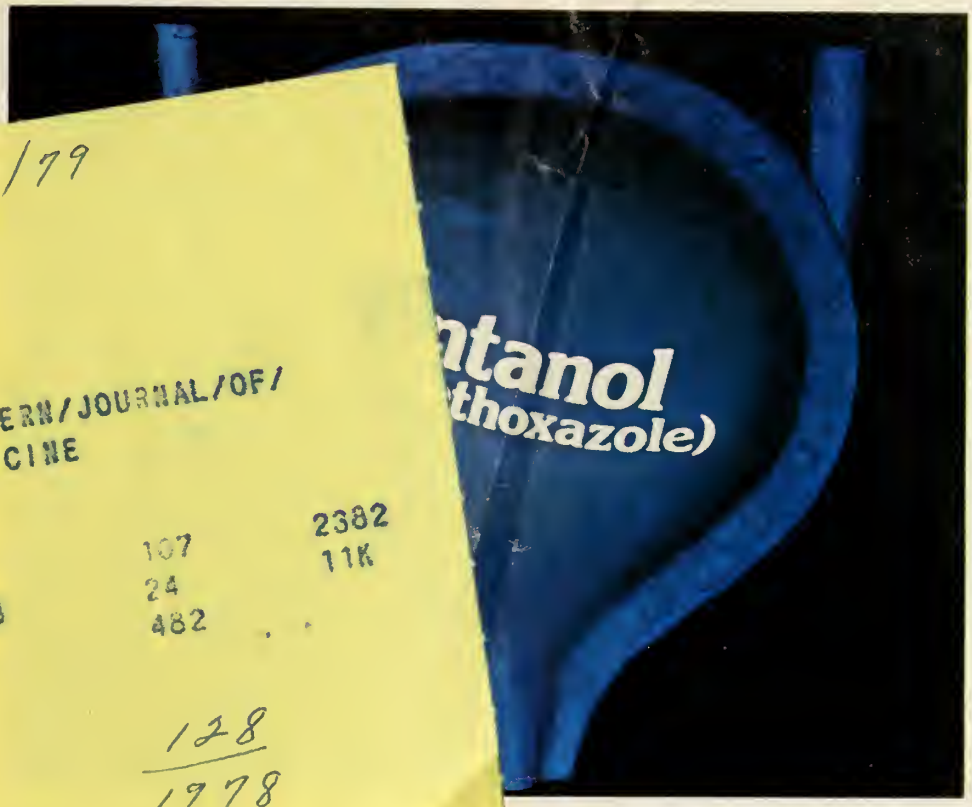

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Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period, infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma, in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). *Usual adult dosage:* 2 Gm (2 DS tabs or 4 tabs or 4 teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection. *Usual child's dosage:* 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

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Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

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Description: Each sugar-coated tablet supplies 5 mEq. of elemental potassium (as potassium gluconate 1.17 Gm.). Kaon Tablets are sugar coated, not enteric coated, which favors dissolution in the stomach and absorption before reaching the small intestine where the lesions with enteric potassium chloride have occurred. The sugar coating merely adds to palatability and ease of swallowing, not to delay absorption as does the enteric coating.
Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. It may be used in the treatment of cardiac arrhythmias due to digitalis intoxication.
Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.
Warning: There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides or certain other oral diuretics. These small-bowel lesions have caused obstruction, hemorrhage and perforation. Surgery was frequently required and deaths have occurred. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Coated potassium tablets should be used only when adequate dietary supplementation is not practical.
Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentra-

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1977

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tions of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

In hypokalemic states, especially in patients on a salt-free diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation. In these circumstances, Kaon (potassium gluconate) should be supplemented with chloride. Ammonium chloride is an excellent source of chloride ion (18.7 mEq. per Gram), but it should not be used in patients with hepatic cirrhosis where ammonium salts are contraindicated. Other sources for chloride are sodium chloride and Diluted Hydrochloric Acid, U.S.P.

It should also be kept in mind that ammonium cycle cation exchange resin, sometimes used to treat hyperkalemia, should not be administered to patients with hepatic cirrhosis.

Adverse Reactions: Nausea, vomiting, diarrhea and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

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Indications: See Kaon Tablets.

Precautions: See Kaon Tablets.

In hypochloremic alkalosis, potassium replacement with potassium chloride (e.g., Kaochlor® 10% Liquid) may be more advantageous than with other potassium salts.

Adverse Reactions: See Kaon Tablets.

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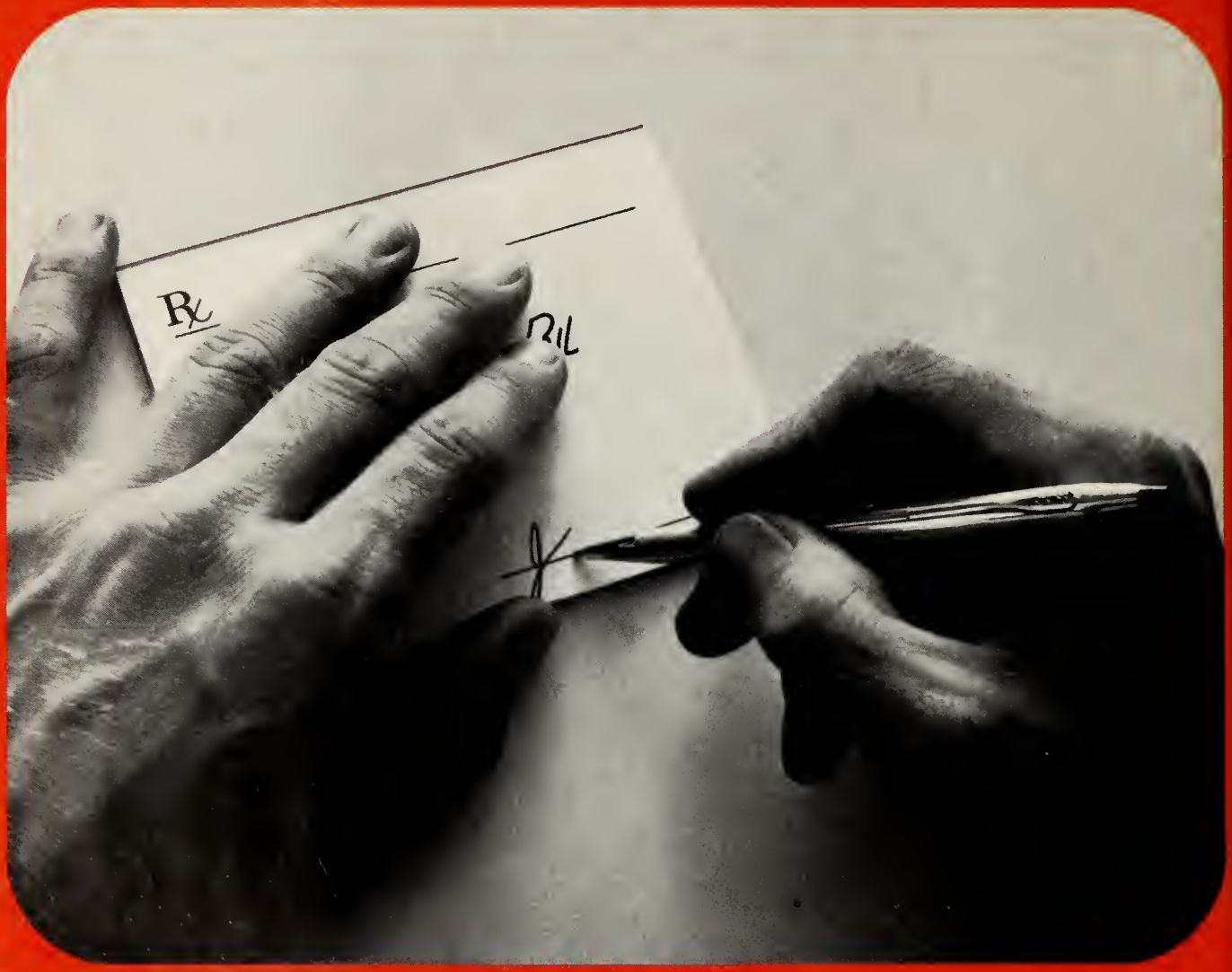
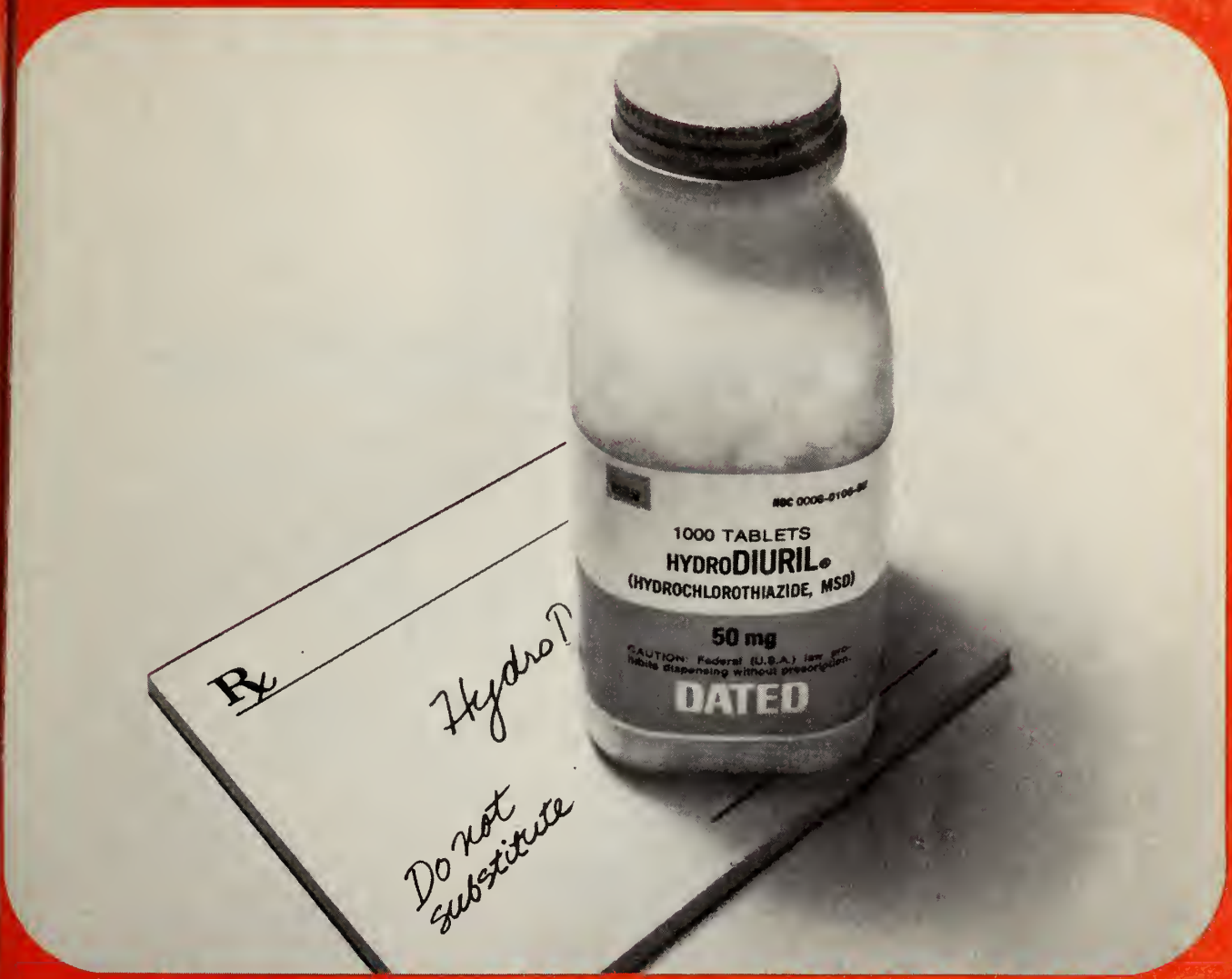


yours...

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs.
Warnings: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy. *Use in Pregnancy:* Thiazides cross placental barrier and appear in cord blood; in pregnancy, weigh anticipated benefit against possible hazards to fetus, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults. *Nursing Mothers:* Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.
Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in post-sympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal im-

for experience—



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pairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.
Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.
Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.
Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).
Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.
Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Tablets containing 100 mg hydrochlorothiazide each in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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NUTRITIONAL RELATIONSHIPS TO DEGENERATIVE DISEASES

DENIS BURKITT, MD, Department of Morbid Anatomy, St. Thomas's Hospital Medical School, London, England.

SOCIAL, ECONOMIC AND POLITICAL IMPLICATIONS OF THE LRI PROGRAM

GEORGE McGOVERN, U.S. Senate; DENIS BURKITT, MD; LOUIS JUNKER, PhD, Department of Economics, Western Michigan University, Kalamazoo.

EVALUATION OF LRI INPATIENT PROGRAM—AN ANALYSIS OF 900 PATIENTS (with Questions and Answers) LRI CASE HISTORIES

DAVID ABBEY, PhD, Associate Director, Survey Research Science, Loma Linda; HANS A. DIEHL, Doctor of Health Science, Research Director, with DON MANNERBERG, MD, Medical Director, and LESLIE CERA, MD, FRCP(C), FACP, LRI Staff.

HIGH CARBOHYDRATE-HIGH FIBER DIETS AS A THERAPEUTIC REGIMEN FOR DIABETES

JAMES W. ANDERSON, MD, Associate Professor, University of Kentucky Medical Center, Lexington, KY.

DIET THERAPY IN DIABETES

RACHMIEL LEVINE, MD, Executive Medical Director, City of Hope Medical Center, Duarte, CA.

ROLE OF EXERCISE IN CVD PREVENTION AND REHABILITATION

BRUNO BALKE, MD, Emeritus Professor, University of Wisconsin, Prevention and Rehabilitation Unit, Aspen Clinic, Aspen, CO.

OUTPATIENT PROGRAM, DIET AND EXERCISE FOR CORONARY HEART DISEASE

BENJAMIN L. ROSIN, MD, Director Cardiology Department, Torrance Memorial Hospital, Assistant Clinical Professor of Medicine, University of Southern California.

NEW CONCEPTS OF "NORMALITY"—CHALLENGING PREVAILING STANDARDS

HUGH TROWELL, MD, formerly Consultant Physician, Department of Medicine and Pediatrics, Makere University and Uganda Government.

PROJECT REPORTS

2, 3 DPG. JAMES BLANKENSHIP, PhD, Professor of Nutrition, School of Health, Loma Linda University.

CLOFIBRATE. JOE D. GOLDSTRITCH, MD, FACC, LRI Staff.

HDL. CHARLES STEWART, PhD, Research Bio-Statistician, Bio-Science Laboratories, Van Nuys, CA; HANS A. DIEHL, DrHSc, LRI.

LRI DIET COMPOSITION AND ADEQUACY—ANALYSES

ILENE PRITIKIN, Nutritional Planning, LRI.

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* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. Associated **widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

CHILD CARE IN GENERAL PRACTICE—Edited by Cyril Hart, MA, MB, DLitt, MRCGP, General Practitioner, Yaxley, Peterborough. Churchill Livingstone/Medical Division of Longman, Inc., 19 West 44th St., New York City (10036), 1977. 442 pages, $16.00 (softbound).

DEAFNESS—Third Edition—John Ballantyne, FRCE, Hon FRCS (I), Consultant Ear, Nose and Throat Surgeon to the Royal Free Hospital and King Edward VII Hospital for Officers, London; Honorary Civilian Consultant in Otolaryngology to the Army; Churchill Livingstone/Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 250 pages, $8.50 (softbound).

HANDBOOK OF PEDIATRICS—Twelfth Edition—Henry K. Silver, MD, Professor of Pediatrics; C. Henry Kempe, MD, Professor of Pediatrics and Microbiology, University of Colorado School of Medicine, Denver; and Henry B. Bruyn, MD, Clinical Professor of Medicine and Pediatrics, University of California, San Francisco: Director of Child Health and Disability Prevention, City and County of San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 721 pages, $9.00.

HANDBOOK OF POISONING: Diagnosis & Treatment—Ninth Edition—Robert H. Dreisbach, MD, PhD, Clinical Professor of Environmental Health, School of Public Health and Community Medicine, University of Washington, Seattle, and Professor (Emeritus) of Pharmacology, Stanford University School of Medicine. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 559 pages, $8.00.

HOW TO FORM YOUR OWN PROFESSIONAL CORPORATION—Ted Nicholas. Enterprise Publishing Co., 1300 Market Street, Wilmington, DE (19801), 1977. 160 pages, $19.95.

JUST ONE MORE—James L. Free—Edited and updated by Julia Free Wenner. Bull Publishing Co., P.O. Box 208, Palo Alto, CA (94302), 1977. 224 pages, $4.95 (Paperback).

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY—13th Edition—Robert Berkow, MD, Editor; John H. Talbott, MD, Consulting Editor; Members of the Editorial Board: Elmer Alpert, MD; Donald C. Bondy, MD; Philip K. Bondy, MD; Alvan R. Feinstein, MD; Alfred P. Fishman, MD; Allen Morgan Kratz, PharmD; John W. Ormsby, MD; Robert Petersdorf, MD; Dickinson W. Richards, MD (Deceased); Professor Sir Martin Roth, MD, FRCP; W. Henry Sebrell, MD, and Louis G. Welt, MD (Deceased). Merck Sharp & Dohme Research Laboratories, A Division of Merck & Co., Inc., Rahway, NJ (07065), 1977. 2,165 pages, $9.75. (Book may be ordered through medical book dealers or directly from Merck & Co., Inc, Publications Department, Box 2000, Rahway, NJ 07065, $9.75 (plus 55¢ shipping if you wish to be billed).

THE NEUROPSYCHOPATHOLOGY OF WRITTEN LANGUAGE—Joseph H. Rosenthal, MD, Director, Learning Disabilities Clinic, Department of Pediatrics, Kaiser-Permanente Medical Center, Oakland; Assistant Clinical Professor, Department of Psychiatry, University of California, San Francisco. Nelson-Hall Inc., Publishers, 325 W. Jackson Blvd., Chicago, IL (60606), 1977. 168 pages, $12.95.

RECENT ADVANCES IN CARDIOLOGY—Number 7—Edited by John Hames, MD, PhD, FRCP, Cardiologist, St. Barthotomew's Hospital, London. Churchill Livingston/Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 511 pages, $39.50.

RENAL AND ELECTROLYTE DISORDERS—Edited by Robert W. Schrier, MD, Professor of Medicine, University of Colorado School of Medicine, Denver; with 12 contributing authors. Little, Brown and Company, Medical Division, 34 Beacon Street, Boston (02106), 1976. 500 pages, $16.50.

TO BE AN INVALID—The Illness of Charles Darwin—Ralph Colp, Jr., MD, Acting Director of the Psychiatric Section, Columbia University Health Service. The University of Chicago Press, 5801 Ellis Avenue, Chicago (60637), 1977. 286 pages, $15.00.

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DESCRIPTION Each tablet of PERCOCET®-5 contains 5mg oxycodone hydrochloride (WARNING: May be habit forming), 325mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS.

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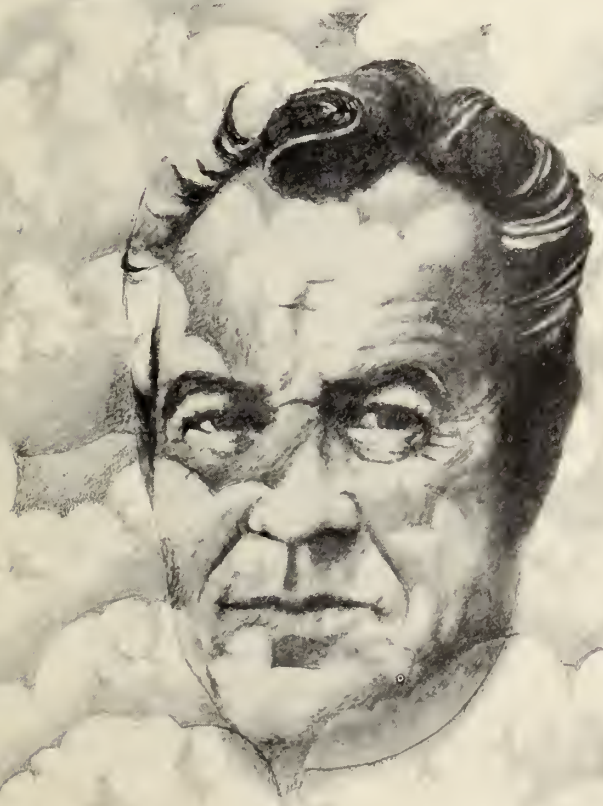

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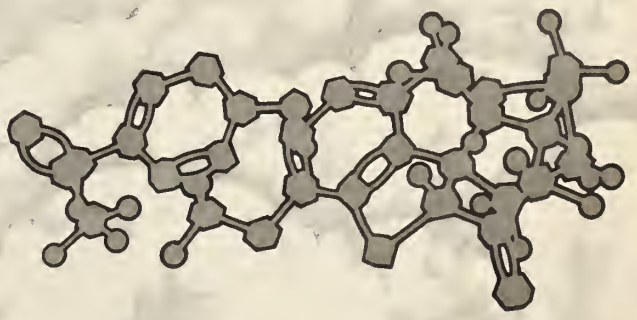

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Please see facing page for Brief Summary of prescribing information.

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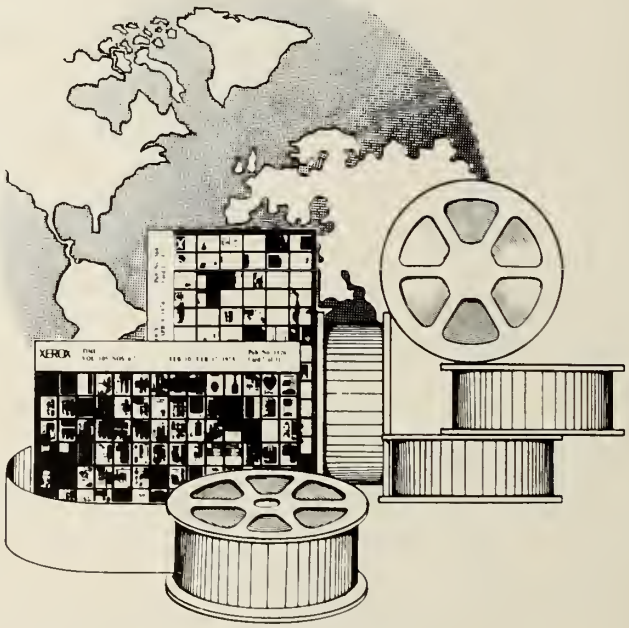

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Tablets contain 5 mg (equivalent to 4.1 mg of free base) or 2.5 mg (equivalent to 2.05 mg of free base) of Brethine, brand of terbutaline sulfate

Indications: As a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Contraindications: Known hypersensitivity to sympathomimetic amines.

Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child

Usage in Pediatrics: Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, and hyperthyroidism. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy

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THE WESTERN
Journal of Medicine

Refer to: Thadepalli H, Francis CK: Diagnostic clues in metastatic lesions of endocarditis in addicts. West J Med 128:1-5, Jan 1978

Diagnostic Clues in Metastatic Lesions of Endocarditis in Addicts

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Gram stains and cultures of multiple extravascular sites showed the infecting organisms in 17 of 26 heroin addicts with endocarditis. In addition to routine blood cultures, the etiologic agent was cultured from Osler nodes and Janeway lesions in ten patients, subcutaneous abscesses in eight, pleural fluids in eight, joint aspirates in three, spinal fluids in three, pericardial fluids in two, muscle abscesses in two and endometrium in one patient. Gram-positive cocci were found in extravascular lesions in 11 of 12 patients with staphylococcal endocarditis and from as many as four different sites. In contrast, no Gram-positive cocci were seen in extravascular sites in any of eight patients with enterococcal endocarditis although six of them had peripheral lesions. Gram stain and culture of multiple extravascular sites appears to provide a valuable early clue to the nature of the etiologic agent in addict endocarditis.

In many medical centers the incidence of addict endocarditis now far exceeds that of classical subacute bacterial endocarditis. The clinical features of these two forms of endocarditis differ; therefore an altered approach both to diagnosis and to management is warranted. In spite of changing patterns, a murmur and a positive blood culture remain as the two imperative criteria for the diagnosis of bacterial endocarditis. In this respect, addict endocarditis may be atypical in that the onset of murmurs is often delayed for many days after a patient is admitted to hospital because of illness. We have found that in many patients later proven to have bacterial endocarditis, aspiration with Gram stain and culture of several extravascular "metastatic sites" provides clues helpful to both diagnosis and management.

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Submitted, revised, July 18, 1977.

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Patients and Methods

During 18 months (July 1973 through December 1974), 26 cases of endocarditis were diagnosed in heroin addicts. In 22 patients the diagnosis was evident at the time of admission or at initial consultation. In four patients, however, the diagnosis resulted from bacterial growth in routine blood cultures obtained, before admission, from a group of 37 patients admitted for heroin detoxification.[2] At least three sets of blood cultures obtained later were also positive. The patients were afebrile and had no pulmonary lesions. In all instances, the diagnosis was confirmed by

characteristic physical findings and results of procedures including cardiac catheterization (7 patients), echocardiography (17 patients), angiography (5 patients), surgical operation (6 patients) and autopsy (3 patients). Multiple sets of blood cultures were positive in all of the 26 patients. Blood culture reports were available at the time of initial consultation in only four patients.

A careful search was made in all patients for Osler nodes, Janeway lesions and subcutaneous abscesses. For the purposes of definition, all erythematous, painful and tender nodular lesions, a few millimeters to a centimeter in size with a somewhat pale center, on the palmar and plantar surface of hands and feet and the tips of fingers and toes were considered as Osler nodes.[3] Those that were not painful were considered as Janeway lesions.[4] Similar lesions on other areas of the body, such as the chest and abdomen, are simply described as subcutaneous abscesses. For control, a smear from adjacent normal skin was also Gram-stained on the same slide. The skin lesions, including Osler and Janeway lesions, were considered positive if the Gram-stained slide prepared from the needle aspirate of the lesion, when examined under oil immersion, showed the presence of both polymorphonuclear leukocytes and bacteria at least once in every three to four fields. They were considered positive when the material aspirated from the lesions had a greater number of bacteria than from the adjacent uninvolved skin used as control.

Gram stain and cultures were done on fluids obtained from Osler, Janeway and other skin lesions; transtracheal aspirates, and aspiration of pleural, spinal and pericardial fluids; results were later correlated with blood culture findings. The criteria for a diagnosis of bacterial endocarditis were (1) at least four sets of positive blood cultures, (2) clearly audible murmurs either on admission or appearing within ten days, (3) fever greater than 38.3°C (101°F) and(or) (4) evidence of metastatic lesions—that is, roentgenographic evidence of pneumonia, cutaneous lesions, microscopic hematuria and a palpable spleen. These criteria were satisfied in all 26 patients. Staphylococcus aureus was identified by colony morphology, coagulase reaction and growth on mannitol-salt agar. Enterococci were identified by gamma hemolysis on the blood agar plates, growth on 40 percent bile, esculin hydrolysis and growth in 6.5 percent salt broth.

Results

Clinical Features

Fourteen men and 12 women aged 21 to 55 were admitted with anemia (85 percent), fever (77 percent), leukocytosis (65 percent). A third of them had no audible murmurs on admission and an additional 15 percent were totally asymptomatic, admitted for detoxification. Eleven patients (42 percent) had left-sided and eight (31 percent) had right-sided endocarditis. Seven patients had endocarditis on both sides. The mitral valve was involved in 12 (46 percent), tricuspid in 10 (38 percent), aortic in 8 (31 percent) and pulmonary in 4 (15 percent). Fifteen patients had pneumonia and eight had empyema. Only four (15 percent) had a palpably enlarged spleen. Seven (27 percent) patients had neurological symptoms such as hemiplegia in five (19 percent), polyneuritis in two (8 percent) and blindness in one (4 percent) (one patient had both polyneuritis and blindness).

Mode of Onset

Endocarditis was the admitting diagnosis in only four out of 26 patients. As noted, four patients were asymptomatic upon admission and were discovered to have endocarditis by routine blood cultures drawn before admission to hospital for detoxification. Bizarre and confusing presentation was not unusual and, in several patients, the initial clinical picture was quite misleading. An extreme example was a young woman with Serratia marcescens endocarditis who was admitted to hospital with suprapubic pain, fever and chills thought to be septic abortion and endometritis. Her lochia was initially reddish in color and this was attributed to altered blood; culture of endometrium yielded a heavy growth of S. marcescens. This organism was also isolated from blood for ten days after curettage and antibiotic therapy. Congestive heart failure was the presenting feature in a diabetic patient, later found to have polymicrobial endocarditis due to Lactobacillus and Enterococcus. All positive culture sources will be described under two categories: intravascular and extravascular.

Intravascular Culture Sites

Staphylococcus aureus was the most frequent causitive organism and was isolated from 12 (46 percent) patients. Enterococcus was the second most common pathogen and was recov-

TABLE 1.—*Extravascular Culture Positive Sites in Addition to Blood Culture*

	Patient																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Causative organism	SA	SA	SA	SA	SA	SA	SA	SA	SA	SA	SA	SA&AS	AS	S	Ps	L&Ec	Eb
Affected valves	M	T	M&T	T	M&T	M	A&M	P	T	M&T	A	T	A		A&M	A	M
Osler & Janeway lesions	:	+	+	+	+	+	+	+	:	+	+	:	+	:	:	:	:
Subcutaneous abscess	:	+	+	:	+	+	+	+	:	:	:	:	:	:	:	*	+
Pleural fluid	:	+	:	+	:	+	+	+	:	:	+	+	:	:	+	+	:
Joint fluid	:	:	+	:	:	:	:	:	:	+	+	+	:	:	:	:	:
Transtracheal aspiration	+	:	:	:	:	:	:	:	:	:	:	:	:	:	+	:	:
Spinal fluid	:	:	+	:	:	+	+	:	:	:	:	:	:	:	:	:	:
Pericardial fluid	+	:	:	+	:	:	:	:	:	:	:	:	:	:	:	:	:
Muscle abscess	:	:	:	:	:	:	:	:	+	:	:	:	:	:	:	:	+
Endometrium	:	:	:	:	:	:	:	:	:	:	:	:	:	+	:	:	:

SA = Staphylococcus aureus
AS = Alpha streptococcus
S = Serratia
Ps = Pseudomonas
L = Lactobacillus
Ec = Enterococcus
Eb = Enterobacter
M = Mitral
T = Tricuspid
A = Aortic
A = Aortic
P = Pulmonary

*Gram-positive rods only, no cocci seen

ered in eight (31 percent) patients. The less frequent isolates were alpha hemolytic streptococcus isolated from two patients, Enterobacter cloacae from two and Serratia marcescens, Pseudomonas aeruginosa, Lactobacillus species and Candida albicans were each isolated from one patient. In all, 28 isolates were found in 26 patients. (In two patients (numbers 12 and 16, Table 1) more than one organism was found in the blood cultures).

Extravascular Culture Sites

Microorganisms were found in extravascular sites in 17 patients (Table 1). In ten patients the Osler nodes and Janeway lesions revealed Gram-positive cocci later identified as Staphylococcus aureus (nine patients) and alpha hemolytic streptococci (one patient). In addition, bacteria other than staphylococci were recovered from subcutaneous abscesses on the chest, abdominal wall and other areas of the body, but were not found in Osler nodes and Janeway lesions. Eight patients had enterococcal endocarditis and, of these, six had peripheral lesions such as subcutaneous abscess in two, arthritis in two and pleuropulmonary lesions in two, but the needle aspirates of these lesions showed no bacteria. Eight subcutaneous abscesses from chest wall, abdominal wall, and muscles of arms and thighs showed the presence of several polymorphs and organisms of singular morphotype: six due to S. aureus, and one each of Lactobacillus and Enterobacter.

The uninvolved portion of the skin rarely showed polymorphs but showed skin flora, mostly cocci once in every ten or more high-power fields examined. Gram stains of joint aspirates showed bacteria in four of the six patients with arthritis of large joints. All four were due to S. aureus. In four patients a pericardial friction rub developed. It was evanescent in two, but in the other two patients pericardial effusions developed which, on aspiration, showed cocci on direct smears and grew S. aureus on cultures. Four women in our study showed evidences for "skin-popping" (subcutaneous injection of drugs). Peripheral lesions due to drug injections were not included in this report.

Cerebrospinal fluid samples were obtained in all seven cases in which there were neurological manifestations. Four were clear and sterile and three were positive for S. aureus. In one patient

with enterococcal endocarditis, sudden onset of monoparesis developed, but the spinal fluid cultures were negative.

Pneumonia or pleural effusion (or both) was the presenting feature in nearly half of the cases. Pleural aspirates in eight patients showed Gram-positive cocci (S. aureus) in seven and Gram-negative rods (Pseudomonas aeruginosa) in one. Transtracheal aspirations (TTA) were carried out in seven patients admitted with pneumonia. This included S. aureus endocarditis in four, enterococcal endocarditis in two and pseudomonas endocarditis in one. The TTA's were smear-positive in all four patients with S. aureus endocarditis. Two partially treated patients were culture negative. The TTA showed Gram-negative rods on smear and grew Pseudomonas aeruginosa in a case of Pseudomonas endocarditis. In two patients with enterococcal endocarditis who were admitted with pneumonia, transtracheal aspirations also were done. In neither instance were organisms seen or cultured.

A simple Gram stain of needle aspirate from various suspected metastatic sites yielded preliminary clues as to the pathogen in 17 patients (65.4 percent).

Discussion

Dr. Mullen of Hamilton, Ontario, was the first to draw the attention of Osler to the skin lesions in endocarditis named after Osler.[3] Osler did not report if these lesions were examined for bacteria, but correctly speculated that "they are in all probability caused by minute emboli." Horder (1909) described 150 cases of infective endocarditis of which 26 percent were reported to have enterococcal endocarditis and 7 percent staphylococcal endocarditis.[5] He noted petechiae in 43 of the 150 (29 percent) cases and saw minute emboli lodged in the arterioles of the skin in all but two cases (these lesions were not cultured). Janeway[4] also described similar ecchymotic eruptions in endocarditis, but did not examine these lesions for bacteria. Blumer (1926) reported Osler's nodes in 19 out of 48 personally observed cases and stated that the "lesion is not pathognomic of the subacute form of bacterial endocarditis" for they were also noted in acute endocarditis due to Staphylococcus aureus.[20]

Nicolous and Poincloux (1929) studied multiple sections of a singular Osler node in endocarditis, but failed to show bacteria by histopathologic examination.[19] Of 167 patients with subacute bacterial endocarditis reported by Pankey (1961), 70 percent had petechiae, 11 percent had Osler nodes and 5 percent had Janeway lesions.[6] They did not report if these lesions were examined for bacteria. Lerner and Weinstein (1966) noted Osler nodes in 23 percent of 57 subacute and none of 43 patients with acute bacterial endocarditis.[8] It is not known if they have examined these lesions for bacteria. Von Gimmengen and Winkelman (1967) also examined the Osler nodes microscopically in two cases, but failed to find bacteria.[20] Louria (1967) and his co-workers recovered Candida stellatoidea from Osler nodes in a case of candidal endocarditis, and Gram-positive cocci in a case of staphylococcal endocarditis.[9] Reyes (1973) and associates reported Osler nodes in acute endocarditis due to Pseudomonas.[10] In a recent case report[11] of staphylococcal endocarditis, large tender pustules with erythematous bases were observed on toes and right palm; aspirates showed Gram-positive cocci.

Peripheral stigmata other than skin lesions in addict endocarditis have also been cultured by others, and pleural fluids,[1,8,10] joint fluids[9,12] and spinal fluids[15] have been positive for microorganisms. Interestingly, most of these isolates were S. aureus, infrequently Gram-negative rods or candida. Like us, others have also failed to recover enterococci from these sites.

The popular impression that Osler nodes are sterile[8,19,20] is not substantiated by well-documented reports. Our experience with 26 consecutively seen patients with addict endocarditis suggests that all skin lesions including Osler nodes and lesions of other extravascular sites are frequently due to septic emboli and, in fact, provide valuable early clues to the diagnosis of staphylococcal endocarditis. Seventeen (65 percent) out of 26 patients in our study had bacteria seen and cultured from skin lesions, subcutaneous abscesses, and transtracheal aspirates or pleural fluids. *All 12 patients with staphylococcal endocarditis had at least one or more smear and culture positive extravascular sites.* Although four of the eight patients with enterococcal endocarditis had these lesions, *none had enterococci seen or cultured from such extravascular sites.* One patient (number 16, Table 1) with enterococcal and Lactobacillus endocarditis had Gram-positive rods identified upon aspiration of a skin lesion, but no cocci.

It has been reported that in addicts Staphy-

lococcus aureus endocarditis develops due to the same phage type as is found in their skin cultures.[16] Therefore, cultures of the skin lesions alone in the absence of positive Gram stains of aspirates of the lesions do not suffice to identfy a metastatic lesion. Gram stain of these lesions, to be significant, moreover, should show on direct examination, pus cells and bacteria in greater number than the adjacent skin. Arbitrarily, a lesion that shows several polymorphs and bacteria in every third or fourth high-power field should be regarded as positive. A negative lesion may have polymorphs, but the number of bacteria may be no greater than those found on the adjacent skin or may, at most, show a single bacterium in every fifth high-power field.

In the present study, five of seven patients had positive transtrachael aspirates (TTA). In all instances, the organisms identified were either S aureus or Gram-negative rods. No bacteria were found in TTA's done in two patients with enterococcal endocarditis. When associated with pneumonia, TTA's appear to be another useful source for the rapid diagnosis of endocarditis. The yield of positive smears and cultures from other extravascular culture sites (joints, pleural and spinal fluids) are shown in Table 1. This aspect was well elucidated in the literature and will not be discussed.

Staphylococcus aureus and enterococci are the major etiologic agents of endocarditis. Therefore, a penicillin or a semisynthetic penicillin is used with an aminoglycoside before results of culture are available. Our study suggests that staphylococcal endocarditis may be readily distinguished from enterococcal endocarditis by simple Gram stain of the needle aspirates of the peripheral lesions when present. In the past this important aspect of endocarditis was underemphasized. Further, enterococcal endocarditis virtually never involves the tricuspid or pulmonary valves. Several other diagnostic techniques were recommended in the past to detect septicemia in endocarditis (for example, serum teichoic acid antibody titres,[15] serum buffy coat examination[16] and intraleukocytic bacteria studies[17]) but these procedures have not been popular and have never come into common use. None of these procedures are as simple and as quick as a diligent clinical examination and a simple Gram stain.

The frequency of classic subacute bacterial endocarditis is now exceeded by that of addict endocarditis in many large metropolitan areas. We emphasize that Osler nodes, Janeway lesions and other innominate skin lesions do occur just as frequently in acute endocarditis in addicts as in the classic subacute disease. Furthermore, these lesions when present, often provide certain important diagnostic and therapeutic clues.

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Refer to: Wilson RL, Rogers WF, Shaub MS, et al: Splenic subcapsular hematoma—Ultrasonic diagnosis. West J Med 128:6-8, Jan 1978

Splenic Subcapsular Hematoma—Ultrasonic Diagnosis

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In five patients with varying histories of blunt abdominal trauma, examinations were carried out with ultrasonography and other imaging modalities. In all five patients, large, fluid-filled masses were noted in the left upper quadrant. Two patients had nonpalpable hematomas, but examinations were done because of history and vague clinical symptoms. Three patients had palpable masses. In all five patients there was surgical confirmation of the ultrasonic findings, and all recovered without complications. Ultrasonic tomography offers a convenient noninvasive method for assessing suspected splenic hematoma and can also exclude the possibility in a careful examination.

THE SPLEEN is the abdominal organ most frequently injured by blunt trauma to this region.[1] The onset of complications such as hemorrhage or hematoma formation varies from a matter of hours to several weeks. The assessment of injury may be conducted on an emergency basis with immediate surgical operation required. In some cases the consideration of splenic injury may be a part of a workup for a seemingly unrelated complaint. Other reports chronicle the advantages and efficacy of other imaging modalities, such as radionuclide imaging[2-4] and selective angiographic procedures.[5-7] Routine radiography may also offer some assistance in the confirmation of a space-occupying lesion in the left upper quadrant or elevation of the left hemidiaphragm.[9] Upper gastrointestinal series and barium enema may be requested to show the extrinsic nature of the mass. Intravenous urograms, while not specific, may be included in the diagnostic protocol and will often show displacement of the left kidney, especially in the presence of large hematomas. All of the foregoing techniques have been used in varying combinations in the workup of a clinically suspected hematoma. They are in the armamentarium of most diagnosticians, but suffer from a lack of specificity in that they show only secondary effects. The true nature or extent of the lesion is not within the capabilities of these classical modalities. One aspect of this limitation arises from the fact that three dimensions of information are integrated or compressed into a two-dimensional format. This is true of most radiographic or radionuclide imaging (Figure 1).

Ultrasonic tomography can offer valuable complementary information in such patients, and can do so without causing concern for hazards or complications of the procedure. It may also be repeated as often as necessary and may be the procedure of choice in pediatric or pregnant patients.

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Submitted March 11, 1977.

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Methods and Material

Diagnostic ultrasound procedures utilize very high frequency sound waves, of short pulse duration, that are beamed into the area of interest through a transducer in contact with the skin. Various tissue interfaces will produce small echoes that are faithfully recorded in a representative position on an image display device. Usually a television monitor is the final viewing device, but its information comes from an electronic memory unit called an image-scan converter. These images show a thin-slice cross section of the region examined and truly represent a vertical tomogram of small but finite thickness. Most commercial scanners available today are capable of recording data to a depth of 30 cm and a width of 40 cm, and can do so in any plane so desired by the diagnostician. Most planes selected are vertical, or near-vertical, with an infinite variety between transverse and longitudinal. The patient, who must usually be transported to the equipment, is placed in the supine, right lateral decubitus or prone position for the examination. Although it is best to carry out the ultrasonic evaluation before the administration of barium,[8] this is not usually a strict requirement in cases of large, space-occupying lesions because the interfering contents of the bowel will probably be displaced from the field of view.

Figure 1.—A posterior view of a technetium Tc 99m sulphur colloid liver-spleen scan. The spleen, depicted on the left side of this view, has a large filling defect in the medial aspect. It is difficult to assess the true size or nature of the suspected lesion.

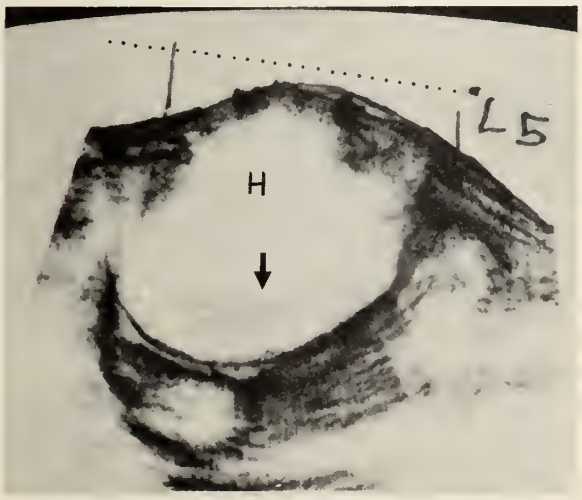

Figure 2.—A longitudinal ultrasonic tomogram of the left upper quadrant in another patient. This view is approximately 5.0 cm from the midline and shows a hematoma **(H)** with a subtle layering of faint echoes **(arrow)** in the dependent portion. It was felt that this represented a gravitational effect on the internal tissue components such as blood cells and debris. The range markers are spaced 1.0 cm apart.

Results

In the series of five patients, examinations were done over 12 months. All patients presented with complaints referable to the left upper quadrant. The initial insult occurred anywhere from one to ten weeks before the ultrasonic procedure and included such incidents as falling down, assault, vehicular accidents and the like. One patient (Figure 2) was thought to have a hematoma of the sheath of the rectus abdominus muscle.

A typical example of the ultrasonic examination is shown in Figure 3, which not only shows the size of the cystic mass but the displacement of adjacent organs as well. The surgical specimen of this ultrasonogram is shown in Figure 4.

It was always surprising to see the full extent of the lesion, as shown on the ultrasonogram, when compared with the various radiographic and radionuclide results. The mass was invariably larger than expected when shown by ultrasonic tomography. Surgical correlation was always very close to the dimensions obtained from the ultrasonogram. In four of five patients, the hematoma was removed intact. In the fifth, the hematoma ruptured in surgery.

There were no false-positive or false-negative results in this series of patients and no patient noted any untoward effects or complications as a result of this procedure.

Discussion

The ability of ultrasonic tomography to show normal as well as pathologic anatomy in the body is well established. When available, it should be considered as one of the first steps in the protocol of splenic injury assessment. A positive finding on examination (Figures 2 and 3) should not be immediately followed by surgical operation unless the clinician can be absolutely confident of the diagnosis. A cystic mass in the left upper quadrant can have its origin in the tail of the pancreas, left adrenal gland, left kidney or left lobe of the liver. A large fluid-filled gastric fundus may also simulate a cystic mass in this region. The stomach can be excluded either by nasogastric suction or by placing the patient in the right lateral decubitus position for 20 or 30 minutes and then repeating the examination. An abscess cavity must also be considered. It is imperative, then, that the ultrasonic results be correlated with the clinical history, thorough physical examination, appropriate laboratory data, radiographic procedures and radionuclide images.

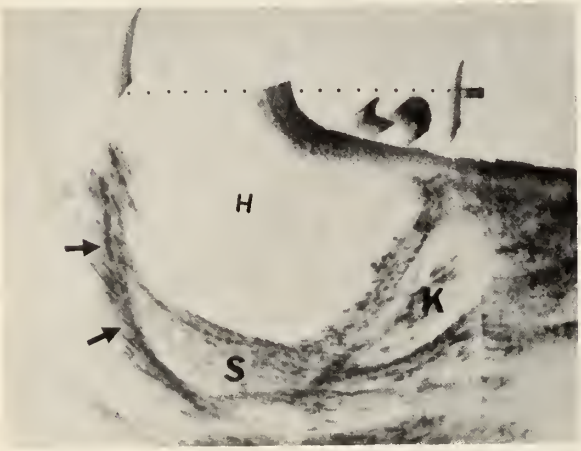

Figure 3.—A longitudinal ultrasonic tomogram of the left upper quadrant, approximately 9.0 cm from the midline. A large echo-free space **(H)** represents the fluid collection or hematoma. The spleen **(S)** is seen to be compressed posteriorly, while the left kidney **(K)** is displaced inferiorly by the hematoma. The left hemidiaphragm is marked by the arrows. The range markers are spaced 1.0 cm apart.

Figure 4.—A photograph of the actual surgical specimen shown in the ultrasonogram of Figure 3. The orientation is similar to its actual position in the patient.

If, however, a careful, meticulous ultrasonic examination in this area fails to show an obvious abnormality, it would then suggest that this patient may not benefit from a vigorous workup and could be observed or followed instead. Of course, the exception may apply in that persistent severe pain or a falling hematocrit reading could stimulate more extreme measures, such as invasive radiography or surgical exploration. The presence of free fluid in the abdomen and a seemingly normal spleen shown on an ultrasonogram may also indicate the need for paracentesis to exclude the possibility of hemoperitoneum.

In summary, the noninvasive modality of ultrasonic tomography should have an integral, initial place in the assessment of possible splenic injury. It, like any other imaging modality, is not without problems, but it does offer an interesting complement to the classical approach.

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Thoracic Outlet Syndrome

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Soft tissue cervical injuries are among the most common posttrauma problems faced by general practitioners, orthopedists and neurosurgeons. The development of the thoracic outlet syndrome (TOS) following such injuries is more frequent than is generally recognized. Conservative treatment with physiotherapy, muscle relaxants, anti-inflammatory drugs and percutaneous electrostimulation usually proves effective in relieving TOS. In this series of 1,958 soft tissue cervical injuries, 459 patients (23 percent) were diagnosed as having TOS. Of these patients, 185 (41 percent) failed to respond to all conservative measures and consequently surgical operation in the form of a supraclavicular neurovascular decompression became necessary to relieve not only the symptoms of the neck-shoulder-arm syndrome but also to relieve a frequently unrecognized (72 percent) vertebrobasilar artery syndrome. The latter is most definitely an integral part of TOS. The most common misdiagnoses were cervical disc syndrome (42 percent) and cervical strain (42 percent). A long-term follow-up (average of seven years) of 90 patients showed that the results were judged good in 75 percent, fair in 11 percent and poor in 14 percent.

During the decade from 1965 through 1975 the author has had the opportunity, in his private neurosurgical practice, to examine 1,958 soft tissue neck injuries. In 459 (23 percent) of these patients a concomitant thoracic outlet syndrome (TOS) developed. Such a high incidence has not been reported previously. A complete bibliography may be obtained from articles by Woods,[1] Lord and Rosati,[2] Kremer[3] and Tyson.[4]

Definition

The term thoracic outlet syndrome is used synonymously with scalenus anticus (Naffziger) syndrome and cervicobrachial neurovascular compression syndrome. TOS can be defined most simply as a syndrome in which there is sufficient pressure on the neurovascular bundle in the supraclavicular fossa or the costoclavicular space, or both, to cause local and distal disturbances of nerve and vascular function. Such pressure may be caused by tightening, fibrosis or hypertrophy of the anterior scalene muscle, the pressure of a cervical rib, narrowing of the costoclavicular space, deformity of the clavicle or first rib, an aneurysm or a tumor, or any other space occupying lesion. Symptoms result from dysfunction of the brachial plexus, phrenic nerve, subclavian artery, subclavian vein, or vertebral artery.

This study of the thoracic outlet syndrome (TOS) arose out of the opportunity this author has had to personally examine and diagnose a large series of soft tissue neck injuries and, therefore, be able to analyze statistically the occur-

Read before the 14th Annual Meeting of the Federation of Western Societies of Neurological Science, Mazatlan, Mexico, February 27, 1977.

Submitted, revised, June 9, 1977.

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TABLE 1—*General Analysis of Cases Reviewed*

Soft Tissue Neck Injuries Studied (1965-75)	1,958
Incidence of Thoracic Outlet Syndrome (TOS)	459 (23%)
Sex Distribution	
Male	29%
Female	71%
Age	
Distribution (years)	10-84
Mean (years)	37
Average Time Lapse Between Injury and Examination	14 months

rence of TOS, its causes, symptomatology and treatment, and to confirm an earlier statement[1] that all too often TOS was not diagnosed before examination.

Table 1 shows an unexpectedly high incidence of TOS (23 percent) following neck injury and confirms the fact that females are far more vulnerable (by a ratio of 2.5 to 1) than males.

By far the most common cause of TOS was a neck injury suffered in an auto accident (61 percent). The ubiquitous rear-end collision, resulting in a "whiplash injury," accounted for 44 percent of the cases. Inevitably these patients became not only therapeutic but medical-legal problems. Accurate diagnosis, including psychological evaluation of the patient and his complaints, was of prime importance because of the intensive legal scrutiny each case underwent. Accuracy of prognosis was of equal importance.

Other causes include industrial accidents, 23 percent; miscellaneous trauma, 8 percent, and unknown, 8 percent.

The diagnosis of TOS would appear to be simple. A patient suffers a musculoligamentous cervical strain (only 8 percent of the patients in this series had no history of neck trauma). The patient is usually not rendered unconscious but states he was "dazed." Neck pain and stiffness increase, and, if the patient is one of the 23 percent in whom TOS develops, he eventually has a combination of the 20 symptoms and signs listed in the order of their frequency in Table 2.

The diagnosis of TOS is often not made because the patient only has complaint of neck and arm pain. He is reticent to reveal other symptoms which he cannot relate to a mere "neck strain." Common among these hidden symptoms are postural vertigo (48 percent), blurred vision (44 percent), difficulty with memory and concentration (31 percent), unsteady gait (18 percent) and syncopal attacks (11 percent). These

TABLE 2.—*Frequency of the Symptoms and Signs of Thoracic Outlet Syndrome*

	Percent
Exact reproduction with anterior scalene pressure	100
Numbness and tingling of hand	99
Neck pain and stiffness	96
Arm pain	94
Weakness of grip	89
Occipital headache	85
Radial pulse signs:	
Adson	7
Reverse Adson	51
Retro-orbital pain	54
Coldness of hand	52
Scapular pain	52
Postural vertigo	48
Blurred vision	44
Difficulty with memory and concentration	31
Reflex diminution	24
Color change of hand	21
Anterior chest pain	21
Unsteady gait	18
Nondermatomal hypalgesia:	
Hand and arm	15
Hand, arm, face and neck	15
Hand alone	10
Hand, arm and neck	5
Syncope ("drop attacks")	11
Tinnitus	6

particular "subjective symptoms," arising from vertebral artery compression, must be elicited from the patient by an experienced examiner. All too often when the patient volunteers such information he is dismissed as having a "functional overlay," or even as a malingerer. The role of vertebrobasilar artery insufficiency, most often brought on by sudden neck rotation or change of posture, is all too frequently overlooked in the patient with TOS.

An accurate history is the sine qua non leading to the diagnosis of TOS. The frequent lack of objective findings on examination was the primary factor for the amazingly high percentage of failure to diagnose TOS in this series (72 percent), in spite of the fact that the time lapse between the original injury and the author's first examination averaged 14 months.

The incomplete clinical diagnosis of "cervical strain" was made in 42 percent of the reports previously sent to referring physicians, insurance companies or attorneys. Of great significance is the fact that another 42 percent of the patients entered for examination with the erroneous diagnosis of "cervical disc syndrome." In 15 patients cervical discectomies had actually been done elsewhere previously. In none of the patients had symptoms been relieved. Following supraclavicu-

lar cervicobrachial decompression there was good relief of symptoms in all 15 of these patients.

The direct or implied previous diagnoses of psychoneurosis, "functional overlay" (5 percent), and malingering (2 percent) were encountered far more frequently in TOS patients than in any other symptom complex encountered in this author's neurosurgical practice. Again, the cause of this discrepancy was failure on the part of the examiners to question the patients, when originally seen, as to the presence or absence of the symptoms listed in Table 2.

Other previous misdiagnoses included carpal tunnel syndrome (2 percent) and others such as "angina" or "stroke" (2 percent).

Another cause for the frequent failure to diagnose TOS is that there is no purely objective diagnostic procedure.

Seventy patients were tested with electromyography and only in 14 percent of these was lower motor neuron dysfuntion reported.

Myelography is, of course, not indicated. It was, however, carried out previously in 49 patients.

Cervical x-ray films were obtained in all of the patients in the series. The only truly diagnostic finding was that of bilateral cervical ribs in eight patients (2 percent). Osteoarthrosis was reported in 36 percent and diminished cervical lordosis in 14 percent. Findings in 48 percent showed no abnormalities.

Electronystagmography (ENG) has a definite value by providing a positive "objective" finding of abnormality in those patients whose postural vertigo, occasional nystagmus and "drop attacks" result from vertebrobasilar artery insufficiency of the medullary vestibular nuclei. This has been reported in detail previously.[5] Electronystagmograms were carried out in 28 patients, with positive findings in 93 percent.

Nerve conduction studies across the thoracic outlet in ten patients failed to show any significant abnormalities.

Subclavian-vertebral arteriograms have proved of little value except in those rare cases where there is a supraclavicular bruit.

Treatment

All patients were treated conservatively with medication—muscle relaxants such as diazepam (Valium®), and anti-inflammatory drugs such as indomethacin (Indocin®), ibuprofen (Motrin®) or naproxen (Naprosyn®). Treatment with physiotherapy was done in 109 patients. This conservative treatment proved to be effective in 50 percent of the cases. The average length of treatment was nine months.

TABLE 3.—*Results of Operative Treatment*

	185 Patients Immediate Follow-up. (Average 4 mos.) (Percent)	*90 Patients Long-term Follow-up. (Average 7 Yrs.) (Percent)*
Good result	81	75
Fair result	16	11
Poor result	3	14

Temporary relief of painful symptoms was obtained by transcutaneous electrostimulation in 75 percent of the 40 patients in which this modality was used. Very little relief was obtained with acupuncture. Most patients were made worse temporarily by cervical traction.

The operative procedure employed is carried out using endotracheal anesthesia, with the patient's head and neck turned and extended to the side opposite the TOS. An incision averaging about three inches (7.3 cm) is made paralleling the skin lines one finger's breadth above the clavicle centering over the anterior scalene muscle. The muscle is exposed and its fibers transected by crushing, and, if necessary, cutting in a transverse direction. Following this the cut ends of the muscle, which is under tension, will retract. The posterior capsule of the muscle and the confluent cervical fascia are dissected, exposing the underlying subclavian artery and brachial plexus. A periarterial stripping of the subclavian artery is done from the thyrocervical trunk to the thoracic outlet, making certain that there are no constricting fascial fibers remaining. A complete lysis of the brachial plexus is done, again making sure there are no constricting fascial fibers left *in situ*. The head is returned to a neutral position and the subcutaneous tissues and skin approximated in two layers.

In 185 patients (41 percent) there was no response to any form of conservative treatment. These patients, therefore, were considered suitable candidates for surgical intervention in the form of a supraclavicular cervicobrachial neurovascular decompression.

Immediate results of operations (see Table 3) were judged to be good in 81 percent, fair in 15 percent and poor in 3 percent. The average length of office follow-up was four months.

Since it is well known that operations for in-

tractable pain frequently offer only temporary relief, and because there has never been a long-term follow-up of patients who have undergone a "scalenotomy," an attempt was made to contact the 185 patients in this series in whom operations were carried out between 1965 and 1975. It was possible to contact 90 of the patients by means of a questionnaire. The results are presented in Table 3 and compared with the results noted at the time of the last postoperative office visit. It can be seen that although the good results dropped from 81 percent to 75 percent and the poor results rose from 3 percent to 14 percent the overall postoperative results have been most satisfactory.

In the 12 patients (14 percent) who were judged to have had a poor result following decompressive operation, a chronic localized brachial plexus neuritis almost invariably developed. In addition, these patients also had the symptoms of a widespread chronic "fibromyositis" which had arisen out of their initial trauma. Often a slightly elevated blood uric acid value was noted. Intensive treatment with colchicine and probenecid, the corticosteroids (prednisolone and the like) and other anti-inflammatory medications (Indocin, Motrin and Naprosyn) invariably failed to relieve the posttraumatic myositis or the postoperative localized neuritis. Occasional temporary relief could be obtained with the use of transcutaneous electrostimulation.

In eight patients scalenotomy had been done elsewhere and had failed to relieve TOS. Operations were carried out again in these patients via the previous supraclavicular approach. Six were found to have had inadequate lysis of the brachial plexus and decompression of the subclavian artery. Fine, tight fibers of cervical fascia were found still compressing the neurovascular bundle. The results of reoperation were judged good in all six patients. In the remaining two patients postoperative scarring was found. In these TOS was relieved by a complete decompression.

The question of which surgical approach, supraclavicular or transaxillary, is preferable for relief of TOS would seem to depend on the surgeon's training. Thoracic and vascular surgeons prefer the transaxillary technique, usually with removal of the first rib. The author, a neurosurgeon, still prefers the original supraclavicular approach because of the smaller (average 7 cm) incision, the more direct exposure of the scalenus anticus muscle and the underlying neurovascular structures, the infrequency of pulmonary complications such as pneumothorax or postoperative pleuritis, and the minimal postoperative morbidity and incisional pain. For success, both operative techniques must accomplish complete periarterial stripping and freeing of the compressed subclavian and vertebral arteries and lysis of the brachial plexus. Excision of a cervical rib can be readily accomplished by either method. Excision of the first rib (rarely necessary), and relief of the costoclavicular syndrome (also rare), can best be accomplished by the transaxillary approach.

Postoperative complications were rare. In five patients temporary dyspnea developed due to trauma to the phrenic nerve at the time of operation. Wound infection occurred in two patients. Local hemorrhage necessitating operative hemostasis occurred in one patient.

Discussion

The concept that the development of TOS following cervical trauma is due solely to pressure on the brachial plexus and subclavian artery by the overlying scalenus anticus muscle and its surrounding cervical fascia must be revised to include the symptoms resulting from vertebral artery constriction, namely postural vertigo, blurred vision, difficulty with memory and concentration, syncopal attacks, nerve deafness and tinnitus. This vertebral artery constriction is the result not only of direct mechanical compression, but most probably due also to dysfunction of the arterial autonomic nerve supply via the vertebral nerve.[1]

The frequency of occurrence, the long period of convalescence, the financial loss through disability and the inevitable medical-legal complications all make TOS one of the most prevalent and important posttraumatic problems faced by the medical profession.

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Refer to: Grundy SM: Cholesterol metabolism in man (Medical Progress). West J Med 128:13-25, Jan 1978

Cholesterol Metabolism in Man

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Recent investigations on cholesterol metabolism in man have led to new insights into diseases associated with abnormal accumulations of cholesterol in plasma (hypercholesterolemia), arterial tissues (atherosclerosis) and biliary tract (gallstones). Regulation of cholesterol synthesis under the influence of dietary and plasma cholesterol, may play a crucial role in determining biliary and tissue concentrations of this sterol. Plasma concentrations, on the other hand, appear to be controlled by complex mechanisms for secretion, transformation and removal of plasma lipoproteins. The recent identification of specific cellular receptors for uptake of plasma lipoproteins represents a significant advance for the understanding of regulation of both plasma and tissue concentrations, and possibly of the basic mechanisms underlying accumulation of cholesterol in atherosclerotic plaques.

ALTHOUGH CHOLESTEROL is a precursor for life-sustaining steroid hormones and a vital substance for cellular integrity, its insolubility in aqueous solutions creates numerous problems for its transport and excretion. Because of its low solubility, special mechanisms are required for transport of cholesterol from one site to another in the body. These include lipoproteins for plasma transport, binding proteins for intracellular transfers, and micellar solutions for biliary excretion and intestinal absorption. Despite the efficiency of these systems, precipitation of cholesterol cannot always be prevented. Therefore, deposition commonly occurs in the arterial wall as an initiating factor for atherosclerosis, and precipitation in bile leads to cholesterol gallstones. In this review basic pathways of cholesterol metabolism in man will be discussed, and in light of recent and important observations in this field speculation on pathogenesis of disorders of cholesterol metabolism—atherosclerosis and gallstones—will be presented.

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Cholesterol Absorption

Cholesterol enters the intestinal tract from two major sources—the diet and bile. A third possible source is secretion by intestinal mucosa. Intake of cholesterol in the American diet, which is derived entirely from animal foods (meat, eggs, milk, cheese and the like) averages 500 to 750 mg per day, but an even greater source of intestinal cholesterol is the bile. In people of normal weight biliary outputs of cholesterol range from 750 to 1,250 mg per day.[1,2] Amounts secreted by intestinal mucosa are much smaller, but have not been measured accurately. Although cholesterol in bile is unesterified, a small fraction from the diet may be in the form of esters in which cholesterol is linked with a fatty acid; however, any cholesterol ester entering the intestine is hydrolyzed rapidly by pancreatic cholesterol esterase.[3]

ABBREVIATIONS USED IN TEXT

CoA = coenzyme A
EHC = enterohepatic circulation
FFA = free fatty acids
HDL = high density lipoproteins
HMG CoA = β-hydroxyl-β-methylglutarate
IDL = intermediate density lipoproteins
LCAT = lecithin-cholesterol acyltransferase
LDL = low density lipoproteins
VLDL = very low density lipoproteins

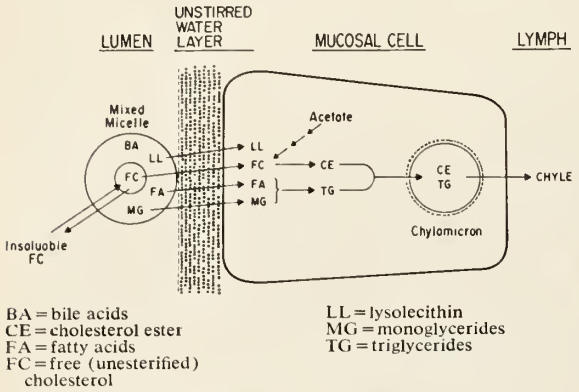


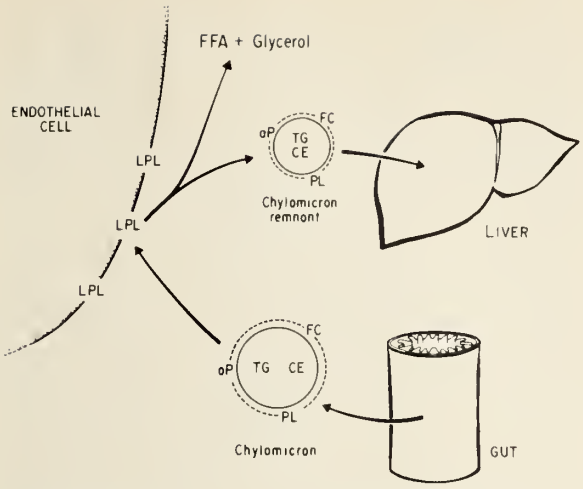
Figure 1.—Mechanisms of cholesterol absorption.

Mechanisms for cholesterol absorption are shown schematically in Figure 1. Before absorption, cholesterol must be solubilized by mixed micelles containing conjugated bile acids and hydrolytic products of triglycerides and lecithin—fatty acids, monoglycerides and lysolecithin.[4,5] Free (unesterified) cholesterol is dissolved in the hydrophobic center of the micelle. Bile acids are crucial detergents of the micelle; they are, in fact, obligatory for cholesterol absorption and when they are diverted from the intestine, as in total biliary obstruction, no cholesterol is absorbed. Even when bile acids are present, however, cholesterol absorption is incomplete; most reports indicate that only 30 to 60 percent of intestinal cholesterol enters body pools.[7-9] Since cholesterol must be in a soluble state before it can be absorbed, the primary factor limiting absorption, in most cases, is the amount of cholesterol that can be solubilized by micelles. Complete absorption of cholesterol is not possible because—in contrast to glucose and amino acids, for example—cholesterol in intestinal contents is never completely dissolved. Amounts of intestinal cholesterol that can be absorbed depend on intraluminal availability of bile acids and hydrolytic products of dietary fats, all of which can expand mixed micelles and promote absorption.[10,11] Maximum absorption of cholesterol occurs in the upper intestine where micelles are swollen by fatty acids and monoglycerides; absorption is less in the lower intestine, possibly due to disruption of micelles by fat absorption.[12]

In addition to solubilizing cholesterol, micelles promote its absorption by facilitating transport across the unstirred layer of water adjacent to the surface of the luminal cell.[13,14] This transport occurs by simple diffusion. Movement through the unstirred layer, and not penetration of the microvillus membrane, appears to be rate-limiting for cholesterol absorption. The micelle as a whole does not penetrate the cell membrane, and passage of cholesterol through structure lipid of the membrane occurs by monomolecular passive diffusion. Whether micelles specifically facilitate cholesterol uptake into the mucosal cell has not been determined, but the requirement of bile acids for cholesterol absorption suggests such a role.

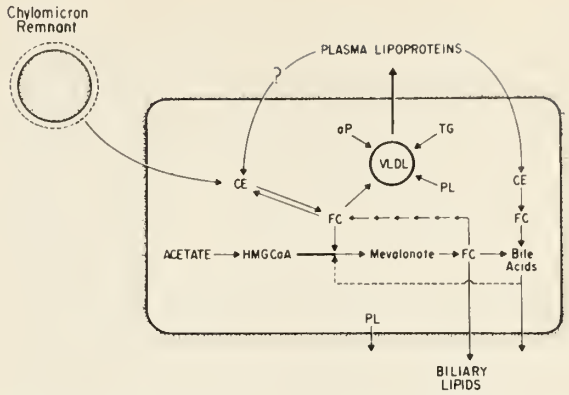
Another group of dietary constituents affecting cholesterol absorption are the plant sterols. These sterols, of which β-sitosterol is the most common, differ from cholesterol only slightly in chemical structure. They interfere with cholesterol absorption,[15] but for unexplained reasons are themselves absorbed in only trace amounts.[16] The plant sterols may decrease cholesterol absorption by more than one mechanism. Therefore, they may, to take three possibilities, displace cholesterol from mixed micelles, compete for its uptake by the mucosal cell membrane and(or) inhibit its esterification in the mucosa, thereby preventing its incorporation into chylomicrons. Normally, the diet contains relatively small amounts of plant sterols (200 to 300 mg per day), and in these amounts they probably retard absorption of cholesterol only minimally. When administered in relatively large amounts (5 to 15 grams per day), however, these sterols inhibit cholesterol absorption amounts completely,[17] and by this mechanism, reduce concentrations of plasma cholesterol.

In addition to lumenal uptake, mucosal cells have the capacity to synthesize cholesterol and in certain experimental animals, such as the rat and baboon, the intestine appears to contribute a significant fraction of the total body production of cholesterol.[18,20] Also, studies have shown that the human intestine can synthesize cholesterol,[21-23] but the level of this synthesis or fraction of total body synthesis is unknown. Amounts of cholesterol produced by the intestine may be regulated



aP = apoproteins
CE = cholesterol ester
FC = free (unesterified) cholesterol
FFA = free fatty acids
LPL = lipoprotein lipase
PL = phospholipids
TG = triglycerides

Figure 2.—Metabolism of chylomicrons.



aP = apoproteins
CE = cholesterol ester
FC = free (unesterified) cholesterol
HMG CoA = β-hydroxyl-β-methyl glutarate
PL = phospholipids
VLDL = very low density lipoproteins

Figure 3.—Hepatic metabolism of cholesterol.

by bile acids, for in the presence of bile acids mucosal synthesis is inhibited[24] and with bile diversion production is enhanced.[21] Presumably, newly-synthesized cholesterol mixes with cholesterol derived from intestinal lumen, and both are absorbed together by the same mechanism.

Before incorporation into chylomicrons most of the cholesterol in the mucosa becomes esterified. The chylomicron particle possesses a lipid-rich core consisting mainly of triglycerides, but also small amounts of cholesterol ester; in addition, it has a surface coat containing protein (including specific apoproteins), phospholipids and free cholesterol. Metabolism of chylomicrons is outlined in Figure 2. They are secreted into chyle and enter the blood stream through the thoracic duct. As they pass into capillary beds these fat particles come into contact with an enzyme, lipoprotein lipase, located on the surface of endothelial cells. This enzyme hydrolyzes triglycerides, with release of free fatty acids and glycerol. And after most of the triglycerides are removed from chylomicrons the remaining particles—called chylomicron remnants—are released into the plasma compartment. These remnants, which probably contain all absorbed cholesterol, are taken up by the liver.[25-27] Newly absorbed cholesterol, therefore, is transported almost exclusively to the liver.

Hepatic Metabolism

Cholesterol in the liver can be derived from three sources: (1) from newly-absorbed cholesterol (delivered by chylomicrons), (2) from peripheral tissues (delivered by plasma liproproteins) and (3) from cholesterol synthesized within the liver cell (Figure 3). Cholesterol that is taken up by the liver, from chylomicrons and other liproproteins, appears to be largely in the form of cholesterol esters[25-28] which can be either stored as esters or hydrolyzed to free cholesterol.

The liver is probably a major source of newly-synthesized cholesterol. While estimates have never been made of daily hepatic production of cholesterol in man, studies in primates suggest that at least half of whole body synthesis occurs in the liver.[23] In persons of normal weight, total body synthesis is in the range of 9 to 13 mg per kg of body weight per day, or for a normal 70-kg man, about 650 to 900 mg per day.[29] If data from nonhuman primates can be extrapolated to man, the human liver would make approximately 325 to 450 mg per day. The precusor for sterol synthesis is acetyl coenzyme A (CoA) and at least 21 steps are in the synthetic pathway for cholesterol.[30,31] Initial steps in cholesterol synthesis include the sequential formation of acetoacetyl CoA, β-hydroxyl-β-methyl glutarate (HMG CoA), and mevalonic acid. The conversion of HMG CoA to mevalonic acid appears to be the rate determining reaction of cholesterol formation. Through a series of condensation reactions, mevalonic acid is transformed into the long-chain hydrocarbon, squalene, which in another sequence of several reactions is cyclized and transformed into cholesterol.

In some way not understood completely cholesterol exerts a feedback inhibition on its own synthesis in the liver.[32-35] The site of feedback inhibition is primarily at the conversion of HMG

CoA to mevalonic acid which is mediated by the enzyme HMG CoA reductase. The activity of this enzyme seems to depend largely on amounts of cholesterol absorbed by the intestine and transported to the liver. The mechanisms by which this inhibition is mediated have not been determined fully. Both allosteric inhibition of the enzyme and reduction of enzyme synthesis are probably involved. Also, the nature of the active feedback agent is in dispute; while it has been generally thought that cholesterol itself is the major inhibitory factor, oxygenated products of cholesterol (for example, 25-hydroxy-cholesterol and 7-keto-cholesterol) have also been found to actively inhibit HMG CoA reductase.[36-40] Whether these latter products are important physiologically remains to be determined.

Although there is a general agreement that cholesterol derived from chylomicron remnants inhibits hepatic synthesis, the feedback potential for cholesterol from other sources is yet to be determined. It is widely assumed, but difficult to prove, that newly-synthesized cholesterol is locally active in feedback regulation; likewise, the activity of cholesterol delivered by plasma lipoproteins other than chylomicrons is uncertain. For example, in familial hypercholesterolemia total-body synthesis of cholesterol is not suppressed contrary to what might be expected.[8,15,29,41] This discrepancy again implies that chylomicron cholesterol is more potent than cholesterol from other lipoproteins in feedback regulation. Furthermore, even within different lipoprotein species cholesterol that is delivered to the liver may vary in potency for feedback inhibition as suggested by Nervi and Dietschy.[42]

Rates of hepatic cholesterogenesis may depend on several factors besides feedback regulation by cholesterol itself. One of these factors may be bile acids. The role of bile acids in regulation of hepatic cholesterol synthesis, however, is controversial and probably complex. The bile acids may influence cholesterol synthesis in at least three ways. First, since bile acids affect cholesterol absorption, an increase of bile acids in the intestine should promote absorption, which in turn will suppress cholesterol synthesis;[35,43,44] a deficiency of bile acids, on the other hand, has the opposite effect, causing increased synthesis. Second, bile acids suppress their own synthesis from cholesterol,[22,45] and should thereby increase hepatic concentrations of cholesterol; this mechanism should reduce synthesis through feedback inhibition by cholesterol itself. Third, bile acids may directly interfere with some step in the biosynthesis of cholesterol,[46,47] although this mechanism is doubted by some investigators. Therefore, actions of bile acids on regulation of cholesterol synthesis are complicated and have not been resolved completely, but they cannot be explained by a single mechanism.

Finally, synthesis of cholesterol in the liver may depend to some extent on food intake. Production rates during feeding considerably exceed those of fasting which may reflect, in part, availability of dietary substrate.[48-50] Furthermore, chronically high intakes of calories are associated with overproduction of cholesterol,[2,51-54] while restriction of calories reduces synthesis.[2] Whether the saturation of dietary fat, independent of total calories, influences cholesterol synthesis is unresolved; in some studies exchange of polyunsaturated fats for saturated fats has been reported to enhance production rates,[41,55-57] but in others, no differences in cholesterol synthesis has been found by exchange of the two fats.[58,59]

As shown in Figure 3, hepatic cholesterol can have three fates: it can be converted partly to bile acids, it can be secreted into bile as cholesterol itself and it can be secreted into plasma with lipoproteins. Transformation of cholesterol to bile acids occurs only in the liver. Normally about a third of the daily production of cholesterol—that is, about 200 to 300 mg per day—is converted into bile acids. The first step in this conversion—the formation of 7α-hydroxycholesterol—is the rate limiting step for production of both primary bile acids: cholic acid and chenodeoxycholic acid.[60-62]

After conjugation with taurine or glycerol, the primary bile acids are secreted into bile and pass through the biliary tract into the duodenum. They are reabsorbed almost completely in the small intestine. While it is generally held that reabsorption occurs mainly in the ileum,[63] recent studies by Hardison, von Bergmann and Grundy[64] have shown that a significant fraction of intestinal bile acids can be absorbed in the upper small bowel. Upon reabsorption, bile acids return via the portal vein to the liver where they are rapidly extracted and resecreted into bile, to complete the enterohepatic circulation (EHC). Because of the high efficiency of reabsorption (about 98 percent),[29] a pool of bile acids which is usually 2 to 3 grams in normal subjects is built in the EHC.

At each turn of the EHC a small fraction of

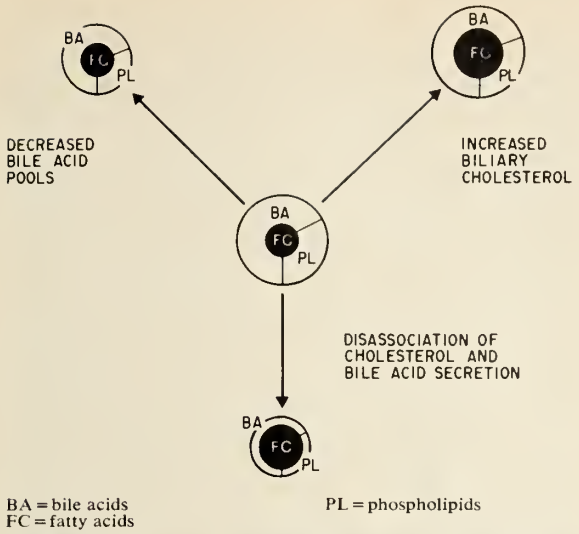


Figure 4.—Causes of supersaturated (lithogenic) bile.

bile acids passes into the large intestine, where, upon contact with colonic microorganisms, hydroxy-groups on their steroid nucleus are altered, producing "secondary" bile acids. Although cholic acid is converted largely to deoxycholic acid, and chenodeoxycholic acid to lithocholic acid, numerous other alterations are possible, and stools may contain a host of secondary bile acids.[15] Appreciable quantities of deoxycholic acid are absorbed in the colon so that it constitutes a significant portion (about a third) of bile acids in the EHC. Lithocholic acid, in contrast, is less well-absorbed, and it normally does not exceed 3 percent of biliary bile acids; most lithocholate in the bile of man is present as its sulfate ester,[65,66] due to its sulfation by the liver.

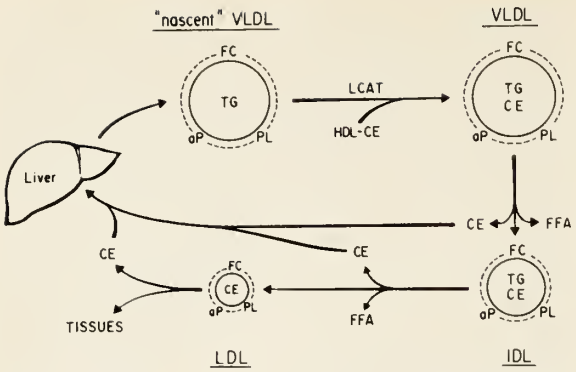
The second fate of hepatic cholesterol is direct secretion into bile. In the steady state, when extrahepatic pools of cholesterol are constant, biliary cholesterol is composed of newly-synthesized cholesterol plus that recycled from the intestine. In adults of normal weight, daily hepatic secretion of cholesterol ranges from 800 to 1,200 mg.[1] As mentioned above, biliary cholesterol enters the intestine along with dietary cholesterol, where 30 to 60 percent is reabsorbed. Unabsorbed cholesterol passes into the colon, is transformed partially into two other neutral steroids—coprostanol and coprostanone[67]—and is excreted with these latter two steroids without reabsorption from the colon.

Metabolism of biliary cholesterol has clinical significance because of the problem of gallstones, which very frequently contain large amounts of cholesterol. The cholesterol in bile is solubilized normally by mixed micelles containing bile acids and phospholipids, but if amounts of cholesterol exceed the solubilizing capacity of these two polar lipids, it is likely to crystallize and initiate stone formation.[68,69] Bile containing excess cholesterol, relative to bile acids and phospholipids, is called supersaturated or "lithogenic" bile. This abnormality may arise in at least three ways (Figure 4). First, there may be a deficiency of bile acids in the EHC (that is, low bile acid pools).[29,70,71] Second, there may be an excess secretion of biliary cholesterol.[2,29,72] Third, in the fasting state secretion of cholesterol may be disproportionately high or dissociated relative to outputs of the solubilizing lipids.[73] In addition, a combination of these abnormalities may coexist in the same patient.

A reduction in the pool size of bile acids has been found in many patients with cholesterol stones; the mechanisms for this abnormality have not been defined with certainty, but a defective regulation of bile acid synthesis appears to be the most likely cause.[29] When patients have an abnormal regulation of synthesis, a decline in pool size and enterohepatic cycling of bile acids resulting from usual daily losses in feces does not release adequately the feedback inhibition on bile acid synthesis, which are required to reexpand the pool to normal levels. A new steady state is therefore established in which bile acid pools are reduced; and although patients with this disorder make and excrete normal amounts of bile acids, they are unable to respond with transitory increments in synthesis that are needed to maintain the bile acid pool in the normal range.

Another cause of supersaturated bile is excessive secretion of cholesterol into bile,[2,29,72] which is usually linked to overproduction of cholesterol within the whole body. Increased cholesterol synthesis is most commonly caused by the high caloric intake associated with obesity. Therefore, the long-recognized association between obesity and gallstones can be explained by enhanced whole-body synthesis of cholesterol.[2] Yet, biliary cholesterol can be increased without obesity,[72] and more studies are needed to determine frequency and importance of this mechanism for production of supersaturated bile in nonobese subjects with gallstones.

Finally, supersaturated bile may arise from abnormal dissociation of hepatic secretion of cholesterol from outputs of its solubilizing lipids



aP = apoproteins
CE = cholesterol ester
FC = free (unesterified) cholesterol
FFA = free fatty acids
HDL = high density lipoproteins
IDL = intermediate density lipoproteins
LCAT = lecithin-cholesterol acyltransferase
LDL = low density lipoproteins
PL = phospholipids
TG = triglycerides
VLDL = very low density lipoproteins

Figure 5.—Plasma transport of cholesterol.

(bile acids and phospholipids).[73,74] According to current theory hepatic cholesterol destined for bile is dissolved first by phospholipids as occurs in many biological membranes, and thereafter, these cholesterol-phospholipid complexes are solubilized by bile acids to form mixed micelles. This mechanism, whereby cholesterol is intimately associated with phospholipids, can explain the finding in several animal species (dogs, rats and monkeys) that cholesterol and phospholipids fall in parallel with declining outputs of bile acids. However, a similar tight coupling of cholesterol and phospholipids does not always occur in man as it does in animals; and when bile acid outputs decline during the fasting state, due to storage of bile acids in the gallbladder, bile saturation with cholesterol can increase to a pronounced degree. This suggests that additional cholesterol which is unassociated with phospholipids can be secreted as well. Cholesterol secretion in man, therefore, appears to occur in a two-step process: first, a portion of biliary cholesterol is presolubilized by phospholipids before dissolution by bile acids, and second, additional cholesterol may be taken up by mixed micelles. In fact secretion of supersaturated bile during fasting almost certainly requires the presence of greater quantities of cholesterol than can be dissolved initially by phospholipids.

Secretion of biliary cholesterol in man, therefore, appears to be more complex than for many animals. This complexity is probably the result of the necessity to dispose of relatively more cholesterol. In comparison with certain animals, such as the dog and rat, man does not have the same ability for transforming cholesterol into bile acids; while these animals convert about two thirds of each day's production of cholesterol into bile acids, man converts only about a third. Man, therefore, is forced to excrete most of his cholesterol as cholesterol itself rather than as bile acids, and this relative "defect" in transformation of cholesterol into bile acids leads to an overloading of the efficient phospholipid-dependent secretion of cholesterol. While most people can cope with the usual loads of newly synthesized and absorbed cholesterol, their secretory processes are of marginal effectiveness and any slight deviation, either because of increased cholesterol synthesis or reduction of bile acid pools, leads to supersaturation and frequently to cholesterol gallstones.

Plasma Transport

A portion of cholesterol produced by the liver is transported to peripheral tissues for utilization. Since cholesterol is completely insoluble in aqueous solution, it cannot circulate freely in plasma and must be brought into solution by more complex mechanisms—specifically by liproproteins. Plasma lipoproteins are complex particles containing well-defined apoproteins, which are proteins that can bind lipids and facilitate their transport from the liver cell to plasma and within the plasma compartment. Basic pathways of lipoprotein metabolism are shown in Figure 5.

The major lipoprotein secreted into plasma is a relatively large particle (300 to 450 A) with a high lipid content that imparts rapid floatation in the ultracentrifuge; hence, the designation "very low density lipoproteins" (VLDL). These particles, which enter plasma in a "nascent" form,[75,76] possess a membranous coat consisting of specific apoproteins, phospholipids and free cholesterol, as well as a nonpolar core containing mostly triglycerides and possibly small amounts of cholesterol ester. When VLDL enters plasma, transformations in its structure begin to occur. The particle first acquires cholesterol ester in its core lipid by two possible mechanisms:[77,78] (1) high density lipoproteins (HDL), which are discussed below, may transfer cholesterol ester directly to VLDL and (2) free cholesterol on the VLDL surface coat can be esterified by the enzyme, lecithin-cholesterol acyltransferase (LCAT).

Degradation of VLDL begins through lipolysis of triglycerides which occurs at the surface of

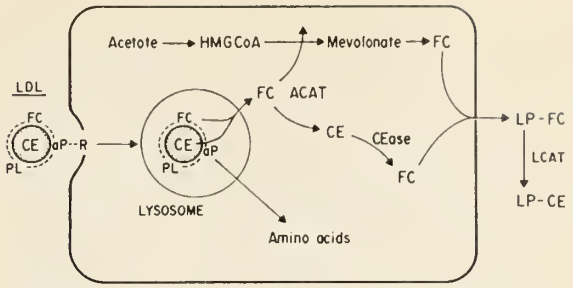
endothelial cells of capillaries; this reaction is catalyzed by the enzyme: lipoprotein lipase. As hydrolysis proceeds free fatty acids (FFA) and glycerol are released, size of VLDL is reduced and density of particles increases so as to yield a product designated intermediate density lipoprotein (IDL). Analogous to the remnant of chylomicron degradation, IDL probably can be taken up *in toto* by the liver of many animal species;[79] in normal man, however, IDL is degraded further to low density lipoprotein (LDL).[80,81] Precise mechanisms for conversion of IDL to LDL are not well understood, but most involve several steps: one is removal of certain apoproteins of the IDL coat; another is elimination of most remaining triglycerides; and finally, a portion of cholesterol ester appears to be removed. The site of removal of excess lipid and protein components has not been determined with certainty, but the liver may play a role.

The LDL particle size is in the range of 175 to 225 A; this lipoprotein contains mostly cholesterol ester in its core lipid with a single protein, apoprotein B, in its membranous coat. The fate of LDL has become a subject of great interest. Until recently, it was assumed that removal and degradation of LDL occurred in the liver;[82,83] this pathway has been brought into question, however, by Sniderman and associates.[84] These workers showed that in pigs LDL degrades normally even after hepatectomy; they suggested, therefore, that other tissues besides the liver may remove LDL, and this suggestion has been amply confirmed as will be discussed in the subsequent section.

Despite peripheral uptake and degradation of LDL, the liver may still dispose of a portion of the cholesterol on circulating lipoproteins. Thus, as VLDL and IDL are degraded some cholesterol ester is released and may go to the liver; also, recent studies by Sniderman[85] in humans have shown that the cholesterol ester content of LDL is decreased with passage across the splanchnic bed, which suggests that LDL cholesterol ester can be removed partly by the liver. If confirmed, this mechanism could be an important means for transport of cholesterol from lipoproteins or tissues to the liver.

Tissue Metabolism

Through recognition of extrahepatic degradation of LDL Sniderman and co-workers[84] focused attention on other sites of LDL uptake, and almost simultaneously Goldstein and Brown[86] observed



aP = apoproteins
ACAT = acyl CoA cholesterol acyltransferase
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FC = free (unesterified) cholesterol
HMG CoA = β-hydroxyl-β-methyl glutarate
LCAT = lecithin-cholesterol acyltransferase
LDL = low density lipoproteins
LP = lipoproteins
PL = phospholipids
R = specific receptor

Figure 6.—Cholesterol metabolism in peripheral tissues.

degradation of LDL by cultured human fibroblasts. These initial studies were followed by intense investigation of metabolism of LDL and cholesterol in cultured cells. Important studies in this area have been carried out by Goldstein and Brown,[86,89] Steinberg, Weinstein, Carew and associates,[90,91] Stein, Stein and co-workers,[91-93] Avigan,[94] Fogelman, Edwards, Popjak and co-workers,[95-99] Ross[100] and Bierman and associates.[101] The following is a brief summary of the results of these investigations.

Basic steps in uptake and degradation of LDL by peripheral cells are shown in Figure 6. First, it should be emphasized that cholesterol is a major component of all mammalian plasma membranes, and one of the functions of plasma lipoproteins may be to provide membrane cholesterol for growth and survival of cells. The steps shown in Figure 6 thus represent essential mechanisms for intracellular cholesterol homeostasis; they have been shown to apply to cells from a variety of tissues including fibroblasts, smooth muscle cells, endothelial cells, polymorphonuclear leukocytes and lymphocytes.

Uptake of LDL by cells appears to be mediated by LDL-binding receptors on the surface of cells. The extent of binding is a function of the number of receptors, which is regulated in turn by cells' need for cholesterol. If a cell contains an abundance of cholesterol, due to excess LDL in the medium, the production of receptors is reduced, thereby decreasing cellular uptake of cholesterol; in reverse, depletion of cellular cholesterol increases the number of receptors, and uptake is facilitated. The physiochemical nature of the binding between LDL and its receptors has not

been determined; however, there appear to be at least two kinds of receptors: high-affinity and low-affinity receptors. But when LDL binds to high-affinity receptors, it enters the cell by absorptive endocytosis and is incorporated into endocytotic vesicles (endosomes) that fuse with lysosomes. Within the lysosome, the lipoprotein is dismantled: apoprotein B of the LDL coat is degraded to amino acids, and cholesterol esters, containing mostly polyunsaturated fatty acids (linoleic acid), are hydrolyzed by lysosomal acid lipase. The resulting unesterified cholesterol is discharged into the cell cytoplasm, where it can be incorporated into cell membranes, reesterified for storage within the cell, or excreted out of the cell. The esterification reaction, occurring through action of acyl CoA: cholesterol acyltransferase (ACAT), usually attaches a saturated fatty acid (palmititic acid) or monounsaturated fatty acid (oleic acid) to the cholesterol molecule; esterification is apparently stimulated by excess cholesterol to prevent abnormal accumulation of free (unesterified) cholesterol in membranes. Another mechanism for keeping intracellular cholesterol at an optimum level is by inhibition of cholesterol synthesis; inhibition of HMG CoA reductase, the key enzyme regulating cholesterol synthesis, appears to be mediated by an increase in intracellular unesterified cholesterol.

Besides specific receptor uptake of LDL, many cells appear to possess other mechanisms for degrading this lipoprotein. Brown and Goldstein[89] have proposed that LDL can also be incorporated into cells by bulk phase phagocytosis. By this mechanism, the fate of LDL cholesterol appears to be entirely different from that derived by specific receptor uptake. After phagocytosis, cholesterol esters are hydrolyzed, but free cholesterol acquired in this way seemingly does not inhibit HMG CoA reductase or stimulate esterification; instead it is returned into the surrounding medium without affecting the overall economy of cholesterol in the cell.

Discovery of pathways described above were made simultaneously with investigations on the metabolic defect in familial hypercholesterolemia. In this disease, plasma levels of LDL are notably elevated—an abnormality that appears to be due in large part to defective uptake of LDL by tissues. Three related, but different mechanisms have been implicated as causes of severe hypercholesterolemia; these defects have been revealed by studies in patients with related forms of homozygous familial hypercholesterolemia. These studies have been carried out in cultured skin fibroblasts, smooth muscle cells, and lymphocytes from affected patients. In some patients LDL receptors are totally absent; in others they are present but defective; and in the third group, receptors appear normal but cells are unable to internalize LDL. In all three types, LDL uptake is blocked and severe hypercholesterolemia develops. When LDL concentrations become extremely high in these patients an alternate pathway, which has been designated the scavenger path, apparently comes into play. This removal pathway, which maintains constant albeit very high levels of LDL, is probably distinct from the specific pathways and probably belongs to the reticuloendothelial (RE) system. A less severe form of hypercholesterolemia occurs in patients who are heterozygous for familial hypercholesterolemia; these patients possess specific receptors, but in reduced numbers; and while plasma LDL is elevated, their LDL concentrations are only about half those with the homozygous form.

Another defect in cellular cholesterol metabolism in familial hypercholesterolemia has been identified by Fogelman and associates.[96,97] These workers studied activation of cholesterol synthesis from acetate in leukocytes incubated in media containing lipid-free serum, and in comparison of leukocytes of normal subjects and patients with heterozygous familial hypercholesterolemia they found that the latter responded with greater activation of cholesterol synthesis than did normals. The leukocytes from hypercholesterolemic subjects were also found to release more newly synthesized cholesterol into the media than normal, which led these workers to suggest that cells from hypercholesterolemic patients may release cholesterol from cells too rapidly; whether this defect is related to a deficiency of LDL receptors on cells has not been determined.

Reverse Cholesterol Transport

As cellular membranes become saturated with cholesterol through uptake of LDL and internal biosynthesis there is need for removal of unused sterol into extracellular fluid for return to the liver. Mechanisms for the "reverse cholesterol transport" have not been determined with certainty, but several possible carriers have been suggested. Glomset[102] has proposed that HDL may be the agent of transport—a hypothesis that is supported by studies in cell culture by Stein and

associates[92,93] If this mechanism pertains, unesterified membrane cholesterol incorporated into HDL may be either transferred to VLDL through the action of LCAT or returned directly to the liver. Other possible carriers of cholesterol include LDL[85] or another plasma protein not previously recognized to transport lipids.[103] Since 1 to 1.5 grams of LDL-cholesterol are probably taken up by peripheral cells each day, this amount of cholesterol plus that synthesized in extrahepatic tissues must find its way back to the liver in some manner.

Hypercholesterolemia and Atherosclerosis

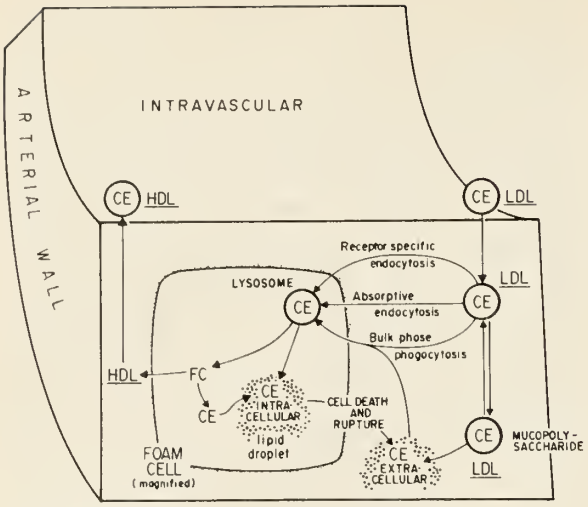
Deposition of cholesterol and its esters in the arterial wall is a major factor in development of atherosclerosis. A portion of cholesterol in atherosclerotic plaques may be derived by local synthesis, but evidence of several kinds indicates that plasma cholesterol is a significant, and probably a major, source. There is, in fact, abundant evidence for a positive correlation between levels of plasma cholesterol and rates of atherogenesis, as shown in a variety of ways for both man and experimental animals. For example, feeding of cholesterol to many species of animals causes hypercholesterolemia and atherosclerosis, and the extent of atherosclerosis usually parallels the rise in plasma cholesterol.[104] Studies in different human populations also have shown that those with high concentrations of plasma cholesterol have more atherosclerotic disease than those with low cholesterol;[105] and within a given population, as in the United States, atherosclerotic disease occurs more commonly in people with the higher levels of plasma cholesterol.[106-108] Furthermore, in familial hyperlipidemias, especially when concentrations of LDL-cholesterol are elevated to a pronounced degree, the incidence of atherosclerotic complications is extremely high.[109-111] Therefore, the relationship between elevated plasma cholesterol and atherosclerosis seems well established.

Because of this relationship, the definition of hypercholesterolemia becomes an important issue. Abnormal concentrations could be defined as those in the upper 5 to 10 percent of a given population. While this method is used commonly, it does not take in account the relationship between cholesterol levels and atherosclerosis. Another approach is to relate plasma cholesterol concentrations to risk for atherosclerosis which should have a more practical or clinical significance. Therefore, a definition of hypercholesterolemia in terms of ideal levels rather than "normal" concentrations would seem more logical and realistic.

According to a normal distribution curve for plasma cholesterol in adult Americans, concentrations greater than 275 mg per 100 ml are usually above the 90th percentile.[112] The Framingham study,[107,112] nevertheless, showed that even below this level cholesterol concentrations are correlated with the prevalence of clinical events related to atherosclerosis. In this particular study, for example, men with plasma cholesterol less than 190 mg per 100 ml were at only half the risk for coronary heart disease as those with levels of 190 to 250 mg per 100 ml. It is therefore reasonable to conclude that those with concentrations in the latter range are not entirely normal, and any definition or classification of hypercholesterolemia should reflect the graded correlation between cholesterol levels and atherosclerosis. One way to modify the term hypercholesterolemia might be according to degrees of severity, that is, mild, moderate, and severe; this categorization will be used in this discussion and should provide perspective for both diagnosis and treatment of hypercholesterolemia in clinical practice.

With these criteria, mild hypercholesterolemia could be defined roughly as cholesterol concentrations of 225 to 275 mg per 100 ml. Causes of mild hypercholesterolemia have not been examined sufficiently, but both environmental and genetic factors probably play important roles. The former include diet (especially diets rich in saturated fats and cholesterol), obesity and possibly lack of exercise. Genetic factors almost certainly can be implicated as well and while the role of heredity has been studied intensively in more severe forms of hypercholesterolemia,[113-115] less attention has been paid to genetic factors in milder elevations of cholesterol. More studies are needed therefore to dissect the relative importance of hereditary and environment in this latter category.

The importance of mild hypercholesterolemia is emphasized by several epidemiologic studies which show that in most patients with atherosclerotic disease there are only mildly elevated cholesterol concentrations.[107,112] Therefore, when consideration is given to the relation between hypercholesterolemia and atherosclerosis, the large number of people with mild hypercholesterolemia should not be overlooked. Actually, however, in mild hypercholesterolemia excess cholesterol may reside in any of several lipopro-



CE = cholesterol ester
HDL = high density lipoproteins
LDL = low density lipoproteins

Figure 7.—Mechanisms of cholesterol deposition in atherosclerosis.

tein fractions and the risk for atherosclerosis may be determined, in part at least, by which lipoprotein fraction carries the excess cholesterol. Since LDL is the most "atherogenic" of all lipoproteins, an increase of LDL-cholesterol probably confers the greatest risk. In patients with associated hypertriglyceridemia, the increment in cholesterol may be largely in VLDL and the role of VLDL in atherogenesis is controversial.[116-119] When VLDL alone is increased with low concentrations of total cholesterol (that is, less than 200 mg per ml), atherosclerosis may not be accelerated.[113,118] In other words, if cholesterol levels are in the ideal range, hypertriglyceridemia per se may not confer increased risk. Finally, in some patients an increase in cholesterol may be contained in HDL. Several recent studies have suggested that people with increased HDL-cholesterol, instead of being at increased risk, may be protected from atherosclerosis,[118,120] possibly through the action of HDL to mobilize cholesterol from the arterial wall.[92,93,102]

Concentrations of plasma cholesterol greater than 275 mg per 100 ml are abnormal by almost any criteria. With *moderate hypercholesterolemia* (plasma cholesterol of approximately 275 to 350 mg per 100 ml) dietary factors may still contribute significantly to the elevation, for many such patients are "dietary responsive" and removal of saturated fats and cholesterol from the diet will produce appreciable reduction in their plasma cholesterol. Hereditary factors, however, are also important in most patients with moderate hypercholesterolemia; at least two "monogenic" disorders, familial combined hyperlipidemia[114,115] and familial hypercholesterolemia,[113-115] as well as a polygenic form of hypercholesterolemia,[114,115] can increase plasma levels to this range.

By present criteria, sustained cholesterol levels greater than 350 mg per ml may be called *severe hypercholesterolemia*. When serum cholesterol is notably increased, regardless of what lipoprotein fraction it is found in, atherogenesis is greatly accelerated. The causes of severe hypercholesterolemia are largely genetic, and dietary factors are usually of lesser importance. The most common cause is familial hypercholesterolemia, but less commonly this degree of elevated cholesterol can occur in familial combined hypercholesterolemia or polygenic hypercholesterolemia.[114,115]

Mechanisms by which plasma LDL-cholesterol may accumulate in atherosclerotic plaques is shown in Figure 7. These mechanisms, which are based on current concepts of LDL metabolism, are largely speculative and further investigation will be required to determine the relative importance of each pathway as well as to uncover new ones. In the diagram, sites of cholesterol accumulations are depicted as cholesterol esters, but at each site there is also an excess of free cholesterol.

Lipoproteins, especially LDL, presumably enter the subintimal space by diffusion through the intima or from the vasovasorum. Subintimal cells, such as smooth muscle cells or tissue macrophages, may then internalize LDL through several mechanisms. As with other cells in peripheral tissues, LDL can be incorporated into lysosomes of arterial cells following interaction with specific receptors on the cell surface (receptor-specific endocytosis)—this kind of LDL uptake has been shown for both smooth muscle cells and macrophages studied *in vitro*. Also, nonspecific uptake might occur by either absorptive endocytosis or bulkphase phagocytosis. When excess cholesterol ester accumulates in these cells, by increased uptake of LDL or decreased removal of the ester, they are transformed in ways not well-understood into "foam" cells which have become engorged with numerous lipid droplets. In early atherosclerotic lesions, called fatty streaks, most cholesterol is intracellular and esterified, and its esters contain high proportions of oleic acid. Since cholesterol esters made within cells usually contain mostly monounsaturated fatty acids, this pattern of esterification in fatty streaks suggests that most

of the excess cholesterol esters in foam cells is derived from free cholesterol which had been released by hydrolysis of LDL-cholesterol esters in lysosomes. In other words, the foam cell esters are probably formed by the same pathway described above for normal cells. An alternate mechanism of foam-cell formation could be engorgement and rupture of lysosomes before ester hydrolysis, but if this occurred fatty acids of cholesterol esters should be largely polyunsaturated (for example, linoleic acid) as are present in plasma lipoproteins.

As atherosclerotic lesions develop and mature, large amounts of cholesterol begin to accumulate outside of cells. These depositions contain a higher proportion of unesterified cholesterol than those intracellularly, and they also have a greater portion of polyunsaturated cholesterol esters. The latter observation suggests that deposition of esters from plasma cholesterol occurs directly without previous hydrolysis in lysosomes. Such an accumulation could take place in two ways: first, LDL could be internalized into cells and then be released before hydrolysis, or second, LDL-cholesterol could be deposited extracellularly without cellular uptake. The latter mechanism could be facilitated by interaction of LDL with tissue mucopolysaccharides for it is well-known that certain mucoploysaccharides can precipitate LDL. The possibility that tissue mucopolysaccharides play an important role in precipitation of LDL within the atherosclerotic plaque makes an attractive hypothesis.

The extent of accumulation of cholesterol in atherosclerotic lesions is determined, of course, by the balance between influx and removal of cholesterol, but regulation of neither process is well-understood. Current evidence suggests that hyperlipoproteinemia and hypertension promote influx of lipids into the arterial wall, and by this mechanism accelerate atherosclerosis. Processes for removal of free and esterified cholesterol from the wall remain to be determined. However, HDL could be one factor in removal of cholesterol from the arterial wall because, as mentioned above, patients with unusually high levels of plasma HDL seem relatively resistant to clinical sequelae of atherosclerosis. Findings in studies in tissue culture are in accord with this proposal; HDL has been shown to inhibit uptake of LDL into cells,[120] and it may serve as a receptor for cholesterol released from cells.[102] An important question is, of course, whether human atherosclerotic plaques can be reversed. By reversal of mechanisms for atherogenesis (such as through decreased LDL and increased HDL levels), regression is theoretically possible and has been suggested by results of studies in animals[121] and preliminary results in man,[122,123] but remains to be established with certainty.

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Specialty Conference

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From Pulmonary Rounds at Stanford University School of Medicine

Refer to: Raffin TA, Robin ED, Pickersgill J, et al: Paraquat ingestion and pulmonary injury—Stanford University School of Medicine Pulmonary Rounds (Specialty Conference). West J Med 128:26-34, Jan 1978

Paraquat Ingestion and Pulmonary Injury

JUDITH PICKERSGILL, MD:* The case we are discussing this morning is that of a 47-year-old man who was reported to have accidentally ingested paraquat on the morning of October 20, 1975.

In mid-1974, he had increased urinary frequency and a prostate nodule was detected on physical examination. A biopsy specimen of the prostate was taken and benign prostate hypertrophy was shown. Results of analysis of urine and cultures were negative. Urinary symptoms continued until January 1975, when low back pain developed, radiating into the rectum and into the left hip. Reevaluation was carried out and a hemorrhoidectomy was done, during which a second biopsy specimen of the prostate was taken; it showed poorly differentiated adenocarcinoma. On further evaluation, an elevated acid phosphatase value was noted and a bone scan showed lesions in the shoulders, rib cage, iliac crest and lumbosacral spine. On x-ray studies none of these suspected metastases were seen. On a lymphangiogram, positive left-iliac nodes were shown, but no other apparent lymphatic spread. It was concluded that advanced metastatic, poorly differentiated adenocarcinoma of the prostate gland was present. The patient was in pronounced distress from low back pain. He was referred to Stanford University Medical Center and estrogen therapy was started. Radiotherapy was carried out between mid-May and early June, with 3,300 rads to the lumbar spine and 3,900 rads to the sacrum.

The low back pain continued and the acid phosphatase and alkaline phosphatase levels were rising. An x-ray study of the chest showed mild bibasilar pulmonary infiltrates. Orchiectomy was suggested, but the patient refused the procedure.

EUGENE D. ROBIN, MD:† *What was felt to be the cause of the infiltrates? Was this metastatic disease or was this chronic lung disease of some other kind?*

DR. PICKERSGILL: The pulmonary infiltrates had developed over the previous six months and were felt to represent lymphangitic spread of prostate carcinoma. There was no evidence to support congestive heart failure or other causes of the bibasilar reticulonodular infiltrates.

The patient was forced to stop work in October 1975 because of back pain. His physicians felt he had a good understanding of his disease. He was taking acetaminophen (Tylenol®) for pain and then was switched to meperidine hydrochloride (Demerol®), which intermittently made him nauseated.

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
CPPB = continuous positive pressure breathing
FIO_2 = forced inspiratory oxygen
SOA = superoxide anion
SOD = superoxide dismutase

DR. ROBIN: I hope that you all have read *Cancer Ward* to help you understand the tremendous burden of dealing with a fatal illness. This unfortunate man apparently had unrelenting pain and had mobilized all of his emotional resources to cope with this horrible situation.

DR. PICKERSGILL: The patient's wife said he was still functioning at home. She said he was up and about, doing minor jobs. He was depressed. He continued to refuse orchiectomy, feeling it would not bring him relief commensurate with the trauma of the procedure. Finally, he decided to have the orchiectomy and it was scheduled for November 2. On October 20, he "accidentally" ingested paraquat. The incident occurred in the patient's home. He stated he had recently placed some paraquat in an old soft drink bottle. While drinking a Coca-Cola® he, by error, picked up the wrong bottle and took a drink of the paraquat. He felt burning in his mouth and spit out the liquid. He washed out his mouth with milk then vomited. He did not mention the mishap to any of his family for the rest of the day. He said he vomited intermittently and his mouth was becoming increasingly sore. The following day, he continued to vomit and told his wife he had taken a drink of paraquat by mistake.

DR. ROBIN: *Do you believe the paraquat ingestion was really an accident?*

DR. PICKERSGILL: No. This unfortunate man was in severe, constant pain and had a relentlessly downhill course. It is interesting to point out that when the patient was carefully questioned about how this accident could have come about, he said the paraquat was in a polyethylene container, not a bottle. However, he stated the color of the paraquat was similar to Coca-Cola and he took a swallow of it simply because he was not paying attention.

DR. ROBIN: I believe the temporal relationship between the patient's feelings about an orchiectomy, clearly a difficult decision for him, and his ingestion is quite telling.

DR. PICKERSGILL: His private physician was contacted and after consultation it was decided he should be transferred to Stanford for dialysis.

On presentation at Stanford two days following ingestion, he was in pronounced distress due to the severe back pain. Swallowing was extremely painful. He had no respiratory complaints.

On physical examination, blood pressure was 120/60 mm of mercury, pulse rate was 120 per minute and regular, respiratory rate was 12 per minute and temperature was 38.5°C (101.3°F), taken orally. Eyes were normal without scleral icterus. Mouth and throat were erythematous with multiple small areas of ulceration. Chest was clear to auscultation and percussion, except for some slight bibasilar rales. Cardiovascular examination showed an S_4 gallop. Gastrointestinal examination showed hepatomegaly with a nontender, nonnodular liver 5 cm below the right costal margin, with an overall span of 12 cm. Findings on examination of the back were notable for moderate to severe pain on palpation of the lumbosacral spine. On rectal examination the prostate was found to be firm and moderately enlarged, with nodules on the left. Stool guaiac was negative. Examination of the extremities showed 2+ pitting edema at the ankles. Neurologic examination showed no abnormalities, except for some sensory loss over the left buttock.

Laboratory studies gave the following results: hematocrit, 30 percent; hemoglobin, 9.8 grams per 100 ml; leukocyte count, 12,300 with a shift to the left, platelets 219,000. Serum sodium was 132 mEq per liter; potassium, 3.5 mEq per liter; chloride, 96 mEq per liter; carbon dioxide, 25 mM per liter; blood urea nitrogen, 40 mg per 100 ml, creatinine, 3.2 mg per 100 ml; glucose, 155 mg per 100 ml; serum glutamic oxaloacetic transaminase (SGOT) 135 units per ml with lactic dehydrogenase (LDH) and alkaline phosphatase off the scale. Analysis of urine showed specific gravity of 1.015, 3+ proteinuria, 4+ blood, 1+ bacteria with 250 to 350 red blood cells and 40 to 60 leukocytes per high power field. Arterial blood gas values were: oxygen pressure, 74 mm of mercury; carbon dioxide pressure, 31 mm of mercury; alveolar-arterial oxygen difference, 39 mm of mercury (normal less than 15 mm of mercury); pH, 7.46; bicarbonate, 21.2 mEq per liter on room air. Bony abnormalities compatible with metastatic prostate carcinoma were seen on an x-ray film of the chest. There were (unchanged) bibasilar infiltrates. Electrocardiographic findings

were normal. Sorbitol was administered to induce a catharsis. The nephrology team recommended a forced diuresis and peritoneal dialysis. It was felt that the metastatic carcinoma in this patient might be effectively palliated by future trials of chemotherapy or orchiectomy. Therefore, an aggressive therapeutic approach was taken. Forced diuresis was initiated with normal solution of sodium chloride and intravenous administration of furosemide. However, the patient did not have an adequate diuretic response, even with high doses of furosemide. The patient was felt to be in acute renal failure. Peritoneal dialysis was instituted.

JAMES THEODORE, MD:* *Dr. Raffin, what are the chances of significantly reducing plasma and tissue paraquat levels with peritoneal dialysis 48 hours after ingestion?*

THOMAS A. RAFFIN, MD:† Paraquat can be removed by dialysis. However, the most critical management steps are to rid the gastrointestinal tract of this agent. Immediate lavage, catharsis and instillation of adsorbents (bentonite or fuller's earth) are critical.[1-3] Only 5 to 10 percent of paraquat is initially absorbed from the gastrointestinal tract, so continued absorption must be prevented.[1] Institution of a forced diuresis along with ultrafiltration hemodialysis is probably the management of choice, to begin concurrently with the above treatment.

This patient was first seen at Stanford 48 hours after paraquat ingestion. A catharsis had been initiated. Whether or not adsorbents would have been efficacious is questionable; however, they would have caused no harm. Forced diuresis was not possible, due to paraquat-induced acute renal failure. This is a common problem. Therefore, dialysis was a logical step.

Paraquat can be found in the urine up to 31 days after ingestion and significant levels have been measured in forced diuresis urine and hemodialysis fluid.[1,4] One reason for prolonged paraquat serum and urine levels is that paraquat binds to tissue and specifically accumulates in human lung.[5,6] In this case, peritoneal dialysis was used. The efficacy of peritoneal dialysis in paraquat poisoning is controversial and ultrafiltration hemodialysis is the method of choice at present.[1] Therefore, the institution of dialysis 48 hours after ingestion would be expected to significantly reduce plasma and tissue paraquat levels.

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DR. PICKERSGILL: Peritoneal dialysis was continued. On the second hospital day, the patient began to cough up yellowish-brown sputum, approximately several tablespoons every six hours. Gram stain was unrevealing and cultures grew normal flora.

DR. ROBIN: *Did anybody see alveolar lining cells or macrophages in the sputum; the patient's lungs were probably undergoing severe damage from paraquat? Remember, yellowish or greenish sputum does not necessarily imply infection; it simply can be the result of an inflammatory process.*

DR. PICKERSGILL: We did not notice alveolar lining cells or macrophages in the Gram stain. Possibly we should have used Wright's or Giemsa's stain for better delineation. During the second hospital day, arterial blood gas values deteriorated and the patient began to become tachypneic. Oxygen pressure was 43 mm of mercury, carbon dioxide pressure was 32 mm of mercury, pH was 7.47, bicarbonate was 23 mEq per liter. Fluid balance and cardiac function were stable and we felt that pulmonary decompensation was a result of paraquat poisoning. Although we were worried about worsening the lung damage with increased forced inspiratory oxygen (FIO_2), we added supplemental oxygen to maintain oxygen pressure between 45 and 55 mm. We felt profound hypoxemia would be more deleterious. Our worry about the interaction between oxygen and paraquat stemmed from the articles in the literature suggesting that paraquat's toxicity might be mediated through oxygen free radicals. The production of oxygen free radicals by paraquat is probably enhanced in the presence of a higher FIO_2. Therefore, we wanted to minimize the FIO_2. An x-ray study of the chest showed a pronounced increase in the old bibasilar interstitial infiltrates. Now there were new infiltrates in the upper lung fields.

On the third hospital day, the patient became severely dyspneic. Adequate gas exchange was not possible with supplemental oxygen and so ventilator therapy was decided upon. Unfortunately, a cardiac arrest occurred and the patient died.

DR. ROBIN: *I have two questions. First, with the increasing infiltrates on the x-ray studies of the chest, did you make an effort to keep the patient as dry as possible during peritoneal dialysis in order to minimize the amount of interstitial lung water and, it would be hoped, improve gas exchange? Second, why did you wait to place the*

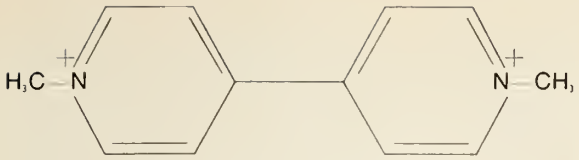

Figure 1.—Structure of Paraquat

patient on a ventilator until supplemental oxygen was not effective in maintaining a reasonably safe arterial oxygen pressure? Don't you feel that the increased FIO_2 *could have been more dangerous than ventilator therapy with a reduced* FIO_2*?*

DR. PICKERSGILL: In response to your first question, we attempted, as best as possible, to keep the patient mildly dehydrated without compromising renal or cardiovascular function.

Your second question is a very good one. I believe it might have been more prudent to have placed the patient on a ventilator when the FIO_2 was being raised to maintain adequate gas exchange. This would have allowed us to minimize the FIO_2. However, we were confronted with the risks of very early ventilator therapy versus the possible risks of a high FIO_2 in paraquat poisoning. We chose the latter, thinking it would be the safest course in this critically ill man.

Postmortem examination was carried out. On gross examination, the lungs were hemorrhagic and contained several firm, greyish-white nodules and areas of infiltrate, which turned out to be metastatic prostate carcinoma. Microscopic examination of the lungs showed areas of hemorrhage, edema, acidophilic material and macrophages in the alveoli. There were many small foci of metastatic prostate carcinoma, and in some areas, what looked like the early changes of fibrosis. Paraquat was detected in blood, urine, tissue and dialysate.

I have asked Dr. Thomas Raffin to make some opening remarks about paraquat poisoning and then Dr. Eugene Robin will conduct the discussion.

DR. RAFFIN: Paraquat (1,1-dimethyl 4, 4′, pyridylium chloride)—the structure of which is shown in Figure 1, is a widely used herbicide, which is inactivated on contact with soil and sold commercially in the United States. It is exceedingly toxic to man in doses as small as 4 mg per kg of body weight. Besides local irritation, and renal, hepatic and myocardial damage, paraquat causes severe injury to the lungs. A *Lancet* editorial in 1971 underscored the growing clinical experience with paraquat ingestions and noted there had been 124 deaths reported up to that time.[7] Also, there had been 60 reported recoveries. The leading cause of paraquat ingestion is attempted suicide. Gramoxone® (20 percent concentrate) is the usual offender, and the less potent commercial product, Weedol®, has not been associated with many fatalities. Ingestion of only 10-20 ml of Gramoxone has been reported to cause death.

Ingestion of large amounts of paraquat leads rapidly to fatal pulmonary edema and hemorrhage, along with renal and hepatic failure. Ingestion of smaller amounts of paraquat can lead to progressive respiratory insufficiency, beginning after several days and sometimes beginning as late as one to two weeks. Of great interest is the fact that the pulmonary pathologic findings in these cases show remarkably early intraalveolar and interstitial fibrosis along with edema, hemorrhage, hyaline membranes and alveolar epithelial proliferation.[8,9]

In the past, paraquat was called a "hit and run" poison, because, in some cases, serum and urine levels were not measurable when toxicity had become clinically apparent.[10] However, the measurement of paraquat levels is difficult and it is known that paraquat is preferentially accumulated in the lungs.[5,6] Also, there are now a significant number of cases where serum and urine paraquat levels have been detected up to two to three weeks beyond ingestion.

The classic clinical presentation in the case of a large ingestion of paraquat is rapid pulmonary insufficiency due to pulmonary edema and hemorrhage. The classic presentation in the case of a smaller, but often fatal ingestion of paraquat—as in the unfortunate man we heard about today—is early pain and ulcerations in mouth, esophagus and stomach. There can be diarrhea and vomiting. Over the first one to three days, acute renal failure evolves. In some cases, jaundice will appear secondary to necrosis of the liver. From several days to one week following the ingestion, respiratory insufficiency develops. The patient will be tachypneic and might be cyanotic. Diffuse infiltrates are seen on x-ray films of the chest. Arterial blood gas studies show hypoxemia and respiratory alkalosis. Pulmonary function studies show decreased lung volumes, low lung compliance and impaired diffusion capacity. At this point, the prognosis is usually poor and the patient will have progressive respiratory insufficiency unresponsive to optimal ventilatory management.

PAUL DAVID LAMAN, MD:* *Do you feel that the metastatic prostatic carcinoma in the patient contributed to the respiratory insufficiency?*

DR. RAFFIN: Yes. The patient had metastatic prostatic carcinoma in both lungs. Bibasilar pulmonary infiltrates were present before paraquat ingestion and those infiltrates had developed over the preceeding six months. The patient probably had lymphangitic spread of carcinoma. He was not tachypneic or dyspneic before paraquat ingestion, but he probably would have become symptomatic in the near future. Therefore, significant pulmonary pathologic conditions already were present. In all likelihood, the areas of metastatic carcinoma were more prone to develop pulmonary edema after paraquat ingestion due to the altered pulmonary architecture. Also, lymphatic drainage of paraquat induced noncardiogenic pulmonary edema would be compromised.

The management of paraquat ingestion is aimed at (1) minimizing paraquat absorption from the gastrointestinal tract, (2) eliminating paraquat that has already been absorbed and (3) modifying the cellular toxicity of paraquat.

As mentioned previously, 5 to 10 percent of paraquat is absorbed. Therefore, a rigorous attempt must be made to remove remaining paraquat from the gastrointestinal tract. Gastric lavage and catharsis should be instituted as soon as possible. The only effective adsorbents are bentonite and fuller's earth.[11] Multiple doses of bentonite are more effective in reducing mortality in rats than single doses.[5] Concurrently, a forced diuresis and ultrafiltration hemodialysis should be initiated. Unfortunately, forced diuresis is often ineffective due to the development of acute renal failure.

LAWRENCE M. SIMON, MD:† *Why do you feel both forced diuresis and ultrafiltration hemodialysis should be used?*

DR. RAFFIN: Large amounts of paraquat have been obtained from both forced diuresis and ultrafiltration hemodialysis.[1] Since it is critical to remove as much paraquat as soon as possible, I do not believe this very aggressive approach is unreasonable. However, it is not at all clear whether ultrafiltration hemodialysis adds anything significantly beyond an effective forced diuresis.

The mechanism of paraquat toxicity probably involves the production of oxygen free radicals, which severely damage the pulmonary parenchyma. Dr. Robin will discuss this and the role of minimizing the inspired oxygen concentration and giving superoxide dismutase with the hope of decreasing the damage caused by oxygen free radicals. Other treatments that have been employed to modify the cellular toxicity of paraquat include using: (1) D-propanolol to compete for cellular receptor sites and thereby increase paraquat excretion, (2) corticosteroids and (3) immunosuppressives.

DR. LAMAN: *What data do you have to support the efficacy of D-propanolol, corticosteroids or immunosuppressives in modifying the cellular toxicity of paraquat?*

DR. RAFFIN: These agents have all been tried on an empiric basis and there are no good data supporting their efficacy. I would not use D-propanolol or immunosuppressives in the treatment of paraquat poisoning until there is evidence of their having a beneficial effect.

DR. PICKERSGILL: Dr. Robin will now discuss some of the interesting pathophysiologic and mechanistic aspects of paraquat poisoning.

DR. ROBIN: Paraquat is a widely used herbicide. The herbicidal potential of paraquat was first realized in 1958. It had been known that compounds similar to paraquat could produce free radicals. The production of free radicals was also known to be the mechanism by which this class of agents acted as herbicides. Paraquat was found to be a remarkably effective herbicide and in a world with increasing requirements for food has been progressively employed in agriculture.

The mechanism of action was felt to be a one electron reduction of paraquat by chlorophyl, producing a paraquat free radical. Then, the paraquat free radical could cause a one electron reduction of oxygen and produce damaging oxygen free radicals. A low oxygen environment reduces the toxicity of paraquat for plants. This understanding of the herbicidal action of paraquat provides insight into the pathogenesis of paraquat toxicity in man. I would like to discuss several aspects of paraquat toxicity.

One aspect involves a misconception in the early literature. Paraquat is not a "hit and run" poison; it is a "stay and hit" poison.

In 1968, paraquat was termed a "hit and run" poison in the literature because toxicity would become clinically apparent when serum paraquat

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levels were immeasurably low.[10] This concept led to much confusion concerning the mechanism of paraquat toxicity. However, in the mid 1970's, it was shown in laboratory animals and *in vitro* that lungs accumulate paraquat selectivity by an energy-dependent process.[5,6]

In rats, guinea pigs, monkeys and, presumably, humans, the administration of paraquat leads to high concentrations of the agent in the lung, despite falling plasma levels. Lung concentrations of paraquat may be 50 times higher than plasma concentrations and the half-life of paraquat in the lung is in the order of weeks, as compared with plasma, where the half-life of paraquat is in the order of hours.

Similar findings have been shown in whole lung slices in the rat. Therefore, despite poor absorption of paraquat from the gut and relatively rapid excretion, there is specific binding of paraquat to lung tissue. This explains several aspects of the disorder. Localization in the lung presumably explains the fact that the agent produces selective pulmonary injury. (Incidentally, a similar compound, diquat, which does not selectively bind to lung tissue does not produce specific pulmonary injury.) Moreover, it explains why injury is independent of plasma levels. It explains continued lung injury after plasma levels are no longer measurable. In this sense, paraquat is a "stay and hit" poison and not a " hit and run" poison.

This aspect of the pathophysiology of paraquat poisoning also has important therapeutic implications. As in all poisonings, immediate and vigorous therapy to remove the poison is mandatory. Absorption and uptake by lung tissue must be minimized. Second, sustained forced diuresis or ultrafiltration hemodialysis (or both) might remove paraquat already bound to pulmonary tissue. However, pulmonary binding is so tight that the above measures may not be particularly helpful. Although I agree with these measures (especially forced diuresis), particularly early in the course, I would not be sanguine about efficacy, especially after major pulmonary binding has occurred.

DR. THEODORE: *Can you suggest any experimental chemicals or treatment that would aid in removing the bound paraquat from pulmonary tissue?*

DR. ROBIN: Dr. Raffin mentioned that the experience with D-propanolol has not been impressive. I know of no other agents or treatment which facilitate the removal of bound paraquat from pulmonary tissue. It would be interesting to try a series of possible blocking agents, using an *in vitro* system (isolated lung slices) to gain additional insight into this possibility.

Another interesting phenomenon is the silent period or incubation period which characterizes clinical paraquat intoxication. A common sequence is the one found in our patient. Following ingestion of moderate amounts, there may be mucosal irritation, gastrointestinal symptoms and minimal pulmonary symptoms. These usually remit and the patient appears to be well for several days. Full blown pulmonary involvement then develops with high protein pulmonary edema, a clinical picture indistinguishable from the adult respiratory distress syndrome (ARDS), progressive pulmonary fibrosis and frequently death from respiratory failure.

Precisely what is occurring during the silent period is not clear. Obviously, paraquat is still present in pulmonary tissue during the silent period. It may be that the silent phase ends when there is sufficient direct lung injury from paraquat to produce clinical manifestations. On the other hand, there are other types of lung injury in which a similar silent period may be found. This is true in radiation pneumonia and in silo fillers' lung (lung injury caused by the inhalation of the oxides of nitrogen [NO_2, N_2O_4]). In these disorders, the toxic agent is no longer present, but lung damage continues. This suggests that continuing lung damage may be related to the release of endogenous agents evoked by the original exposure which continue to produce lung injury independent of the direct toxic effect of the given agent.

In this respect, one patient with paraquat toxicity was treated with pulmonary transplantation. At postmortem examination, the transplanted lung was reputed to show changes consistent with paraquat toxicity.

A major area of interest is the possibility that paraquat produces lung injury by the production of oxygen free radical damage. There has been a great deal of interest in oxygen toxicity over the past two decades. In 1954 Gershman proposed oxygen free radicals as the mechanism of action for the tissue damage caused by oxygen.[12] This hypothesis evolved from observations concerning the similarities between the lethality of ionizing radiation and oxygen toxicity. Ionizing radiation is mediated via oxygen free radicals. It is also felt that oxidant air pollutants produce high concen-

trations of oxygen free radicals. In the last ten years investigators have studied the chemical behavior of oxygen free radicals in mammalian systems. Table 1 outlines the major oxygen free radical species.

Equation 1 in the table shows how the one electron reduction of oxygen forms the oxygen free radical superoxide anion (SOA). Paraquat could reduce oxygen in this way. The second equation shows how the enzyme superoxide dismutase (SOD), found in all aerobic bacteria and mammalian tissues studied, converts SOA into hydrogen peroxide (H_2O_2).[13] It is important to point out that H_2O_2 is quite toxic and bacteria and mammalian systems remove H_2O_2, using catalase or other peroxidases. The most damaging oxygen free radical, the hydroxyl free radical, is formed by the combination of SOA and H_2O_2. This is shown in equation 3 and is known as the Haber-Weiss reaction.

DR. LAMAN: *How do these oxygen free radicals exert their damaging effect?*

DR. ROBIN: Oxygen free radicals can strongly oxidize and reduce other chemical species. They are remarkably reactive compounds. Intermediaries which they produce, such as lipid free radicals in cell membranes (lipoperoxides) are also involved in injury. Three consequences of oxygen free radical and lipoperoxide exposure are: (1) the disruption of cell and subcellular membranes (hydrocarbon chain breakdown), (2) oxidation of enzyme — SH groups (such as isocitrate dehydrogenase, glyceraldehyde-3 phosphate dehydrogenase, and the like) and (3) nucleic acid breakdown. As a result, oxygen free radicals can produce a wide spectrum of cellular structural and functional abnormalities.

The evidence which links the toxic effects of paraquat with increased generation of oxygen free radicals is extensive and paraquat toxicity is widely accepted as a model of oxidant injury. However, it should be pointed out that the pathogenetic relationship is by no means unequivocally established. One implication of the presumed pathogenetic relationship is that paraquat and high oxygen exposure might be expected to have either additive or even synergistic effects. This assumption is the basis for limiting the administration of oxygen to these patients.

The histopathology of human paraquat poisoning is interesting. In severe cases, after several days to several weeks, there is a pronounced intraalveolar fibrosis, often without a prominent interstitial component.[14] Interstitial fibrosis occurs later. This is somewhat different from the findings in oxygen toxicity where usually interstitial involvement occurs early and diffuse intraalveolar fibrosis is not common. Both paraquat and oxygen toxicity have an acute exudative phase with edema, the development of hyaline membranes and cell death (ARDS). However, by electron microscopic study, it appears the initial injury by oxygen involves the capillary endothelium while the initial injury by paraquat involves the alveolar epithelium. Therefore, although both might be mediated by oxygen free radicals early in the pathogenetic sequence, the two disorders have a somewhat different histopathologic pattern. Why paraquat causes earlier alveolar epithelial damage and more intraalveolar fibrosis is not clear, but could be related to the accumulation of paraquat in alveolar epithelium (more local damage to the basement membrane).

Turning now to the practical implications of the relationship between paraquat and oxygen, Fisher and co-workers showed that oxygen potentiates the lethal effects of paraquat poisoning, and they suggested that the use of elevated FIO_2 levels in paraquat poisoning probably should be avoided.[15]

Rhodes and associates showed that mice, after intraperitoneal paraquat injection, survived longer in hypoxic (10 percent oxygen) environments than in room air.[16] Also, when mice in the hypoxic environment were brought into room air, pulmonary edema developed and they died. This study showed hypoxic protection in paraquat poisoning.

I feel there is danger in extrapolating conclusions from these papers for the management of paraquat poisoning in patients. It has not been

TABLE 1.—*Oxygen Free Radicals (see text for explanation)*

1. $O_2 + e^- \longrightarrow O_2^-$ (superoxide anion)
2. $2H^+ + O_2^- + O_2^- \xrightarrow{\text{superoxide dismutase}} O_2 + H_2O_2$ (hydrogen peroxide)
3. $O_2^- + H_2O_2 \xrightarrow{\text{Haber-Weiss Reaction}} OH^- + O_2 + OH\cdot$ (hydroxyl free radical)

shown that exposing a human, who has ingested paraquat, to a lower FIO_2 is worth the risk if one allows the patient to become severely hypoxemic (arterial oxygen pressure less than 50 mm of mercury). This could be a poor trade off.

In the animal studies, exposure to low oxygen levels was in close temporal relationship to paraquat exposure. This is usually not possible in clinical paraquat poisoning.

It should also be remembered that in the animal studies, the end point was the effect of paraquat and oxygen on the lungs. In the intact patient, we must be concerned with the brain and heart and all tissues requiring oxygen. Therefore, an attempt to have a patient survive with an arterial oxygen pressure of 30 to 40 mm of mercury may not be appropriate. However, in the face of paraquat ingestion there is a way to lower FIO_2 and maintain adequate blood oxygenation.

Early intubation and the use of continuous positive pressure breathing (CPPB) could allow lower FIO_2 levels along with a more adequate arterial oxygen pressure. This approach, it is to be hoped, might lessen pulmonary damage while not producing cerebral or myocardial damage due to severe hypoxemia. Of course, prophylactic CPPB in paraquat poisoning has not been investigated by a carefully controlled study and this suggestion is only a speculation. The risks of early intubation and CPPB therapy are real. However, I feel that if minimization of FIO_2 is an important goal, then elective intubation and CPPB therapy is less dangerous than severe hypoxemia.

This suggestion is only a special case of a more general dilemma in many patients with acute respiratory failure. The problem of the best compromise between lowering FIO_2 and using higher levels of CPPB arises frequently. Paraquat poisoning represents a disease in which the data suggest more dependence on CPPB and less dependence on FIO_2. However, arterial oxygen pressure must be maintained at levels compatible with survival.

Given the high mortality associated with paraquat ingestion, one other possible experimental form of therapy may be worth considering. As I mentioned before, the enzyme superoxide dismutase converts the oxygen free radical, superoxide anion, to hydrogen peroxide. Hydogen peroxide, a toxic substance itself, is then removed by catalase or other peroxidases. Therefore, it is theoretically possible that SOD might scavenge superoxide anions and decrease the damage caused by either oxygen toxicity or paraquat poisoning.

Autor, in 1974, used parenterally administered SOD on paraquat-treated rats and found survival to be prolonged in both air and 90 percent oxygen.[17] Animals in air survived longer with SOD than animals in 90 percent oxygen. Also, on microscopic examination, it appeared that there was less damage in the SOD treated rats.

Block and co-workers in 1977, showed that the parenteral administration of SOD both prolonged and increased survival in paraquat-poisoned rats.[18] They also investigated the use of reduced glutathione and D-propanolol, both of which had no effect. As in Autor's study, histologic examination of SOD treated rats compared with controls showed much reduced histopathologic abnormalities. SOD was, however, used in a close temporal relationship to paraquat exposure.

SOD has been used clinically.[1] What is needed is a carefully controlled clinical trial, but due to the sporadic nature of paraquat poisoning, it is highly unlikely that such a study could be adequately conducted. Because paraquat poisoning is so lethal, the use of SOD in individual patients could be supported in carefully documented significant ingestions, based on the Hippocratic dictum "desperate diseases require desperate measures."

Finally, it might be emphasized that pulmonary fibrosis may already be extensive when clinical respiratory insufficiency first develops. In such patients, no form of supportive treatment may salvage the patient.

In conclusion, paraquat is a "stay and hit" poison. It probably acts by producing oxygen free radicals and therefore potentiating oxygen toxicity. We need much more data about the kinetics of binding to lung cells, about the specific cell types to which the agent binds and possible competitive agents which can displace paraquat from its tight binding to pulmonary epithelial receptors.

One therapeutic goal in the management of a patient with paraquat ingestion is to minimize the FIO_2 and possibly minimize the production of oxygen free radicals. However, this should not be done at the expense of severe hypoxemia. A solution might be to electively intubate the patient and use CPPB to minimize FIO_2 and prevent severe hypoxemia. Finally, exogenous SOD has been reputed in animal models to increase survival and prolong life after paraquat poisoning. Although

entirely experimental and potentially harmful, it would be reasonable to use it therapeutically in appropriate patients with paraquat poisoning.

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Long-Standing Ulcerative Colitis

WOULD YOU OPERATE on a patient with ulcerative colitis whose condition is reasonably well controlled medically simply because he has had the disease for more than 10 to 15 years and faces an increased risk of cancer of the colon? . . . We have had to rely to a great extent on the pathologist to tell us whether the hyperplastic changes are getting out of hand, and there has been a great deal of work in trying to decide what the criteria are to indicate this. . . . Certainly anything that is suspicious radiologically should be examined endoscopically. Biopsy specimens should be taken and a decision reached. Although all strictures of the colon and ulcerative colitis are not malignant, I think we have to take the attitude that a stricture appearing after many years of ulcerative colitis must be considered as malignant until it is proved otherwise—and that usually results in colectomy, especially if the biopsy results are equivocal. From a surgical standpoint, since the established cancer in ulcerative colitis has a very poor prognosis (when it's obvious that this is a malignant change, it's usually an advanced lesion), we would like to treat these patients before that has happened. In patients in whom colitis remains active for ten or more years, particularly those in whom a changing pattern is seen on barium x-ray studies (indicating epithelial hyperplasia) and those whose initial symptoms developed at an early age, prophylactic colectomy is a good procedure. In the older age-group I'm not so sure. . . . And I just don't know where to draw the line.

—CHARLES B. RIPSTEIN, MD, *Miami*

Extracted from *Audio-Digest Internal Medicine*, Vol. 24, No. 8, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Valentine WN: Hereditary spherocytosis revisited—Eighth Annual Paul M. Aggeler Memorial Lecture—Medical Staff Conference, University of California, San Francisco. West J Med 128:35-45, Jan 1978

Hereditary Spherocytosis Revisited

Eighth Annual Paul M. Aggeler Memorial Lecture

Delivered October 25, 1977
San Francisco General Hospital Medical Center

WILLIAM N. VALENTINE, MD, *Los Angeles*

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. KREVANS:* I would like to welcome all of you to the annual lecture in the memory of Paul Aggeler, who was an outstanding hematologist and human being. He was a close personal friend of many in this room, and a colleague of mine and many other hematologists. We are privileged this morning to have as the Aggeler Lecturer Dr. William N. Valentine from the University of California, Los Angeles, one of the genuine leaders in the field of academic hematology in the United States today. His published work has ranged from fundamental observations on leukocytes to his recent elegant focus on understanding the erythrocyte. He has made an enormous number of important clinical and fundamental contributions to our understanding of the internal metabolism of red blood cells and the clinical diseases that spring from the disorders of that metabolism.

DR. VALENTINE:† Thank you. I am very pleased and honored to be the Aggeler Visiting Professor for this year. I knew Paul Aggeler well and I admired him very much. He was a man who had a degree of quiet humility and self-effacing qualities that really belied his enormous contributions to medicine. I have entitled my discussion, which is really a review, "Hereditary Spherocytosis Revisited."

History and Introduction

I have on several occasions endeavored to see what makes up blood. I obtained a drop of it from my own hand and I saw it was composed of small round globules, driven through a crystalline humidity of water.

—ANTON VAN LEEUWENHOEK. *Letter. April 7, 1674*

Few hematologic diseases have been investigated with more diligence and ingenuity without yielding their ultimate secrets than has hereditary

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spherocytosis (HS). Leeuwenhoek, the father of hematology, considered that mammalian blood contains "red globules," although his sketches of amphibian blood suggest a biconcave discoidal shape. Most 18th century texts of physiology concurred. This generally held view was convincingly refuted, however, in a paper read by Hewson before the Royal Society in 1773.[1] Although Leeuwenhoek had surmised that a globular shape was most suitable for circulating in the blood vessels, he had not diluted mammalian blood and hence was unable to see its "globules" separately from each other. Hewson, who is perhaps better known for his remarkable contributions to knowledge of the lymphatic system and the coagulation of blood, conducted experiments in which blood was diluted in *its own serum.* His predecessors either used undiluted blood or diluted the blood with water, which "dissolved" the red globules. The red globules, properly diluted in serum, were seen not to be spherical but to be flat like a coin. Successive increments of water added to serum suspensions caused the coin-like particles to assume a constantly more spherical shape until finally they "dissolved" and appeared colorless. Thus Hewson unwittingly carried out the first crude osmotic fragility test. In other experiments it was observed that if neutral salts were added to water in exactly the proper proportions, the flat shape seen in serum suspensions was preserved irrespective of the degree of dilution. Stronger solutions of salt "shrivelled" or crenated the particles. In still other studies, Hewson perceived that under some conditions the red particles were capable of fragmentation into smaller entities, which nonetheless retained their red color. It was thus established two hundred years ago that the normal human red blood cell is a discocyte and not a spherocyte, and that it may fragment without losing its hemoglobin.

More than a century after Hewson's death a congenital disorder characterized by the presence of spherical erythrocytes was conclusively recognized. Although rather excellent prior accounts of the syndrome had been published,[2,3] Minkowski[4] is usually credited with the first accurate clinical description. However, 29 years earlier, the Belgian physicians Vanlair and Masius[2] had reported "microcythemia," described the spherical shape of the red cells and proposed that the cause of anemia in their patient was an abnormally rapid destruction of the erythrocytes. Shortly after the turn of the 20th century, Chauffard recognized greatly diminished resistance of the erythrocytes to lysis in hypotonic saline and prominent reticulocytosis[5,6] as hallmarks of the disease. At about the same time an "acquired" form of hemolytic anemia, also characterized by spherical red cells, was described and became known as the Hayem-Widal type[7,8] in contrast to the congenital Minkowski-Chauffard form. Although a variety of hemolytic states were mistakenly lumped with these entities, the acquired form undoubtedly consisted largely of cases that would be classified today as Coombs-positive autoimmune hemolytic anemia.

In the United States the first case of congenital hemolytic jaundice (there were many other synonyms) was reported in 1910,[9] and by the time of Tileston's monograph[10] in 1922 most of the major features of the disorder had been clearly suggested. Jaundice appeared at birth or during childhood and persisted in a fluctuating manner throughout life. As Chauffard had observed, many patients were more jaundiced than sick and many attained an advanced age. The disease often involved three or more generations, and the sexes were equally affected. Some family members were free of disease and, when this occurred, so were their children. Icterus was usually not intense, and there were no signs of biliary obstruction such as itching, bradycardia, xanthomata or a greenish tint to the jaundice. The urine was notably lacking in bile; the stools were heavily colored, contained excess urobilin, and were never acholic. Enlargement of the spleen was the rule. Anemia was usually modest, reticulocytosis was prominent, and there were occasional "crises of déglobulization" as the French termed it. At times, the crises were accompanied by deepening jaundice, fever, pain over spleen and liver, and a rapidly worsening anemia. Occurrence of gallstones at a young age was common. The red cells were osmotically fragile in contrast to their *increased* osmotic resistance in patients with obstructive jaundice. Hemolysins were almost invariably absent. Splenectomy was being done with "increasing frequency and happy consequences."[10] Following the procedure, a permanent clinical cure was predictable, jaundice rapidly subsided, and anemia and reticulocytosis disappeared. Increased red cell fragility and morphologic abnormalities in the circulating blood persisted, however. In contrast to chronic passive hyperemia in which splenic sinuses were engorged with blood, the congestion in some but not all spleens removed from patients with con-

genital hemolytic icterus was confined to the pulp or "cords of Bilroth," while the sinuses lay empty.[10] All this by 1922.

Hereditary spherocytosis is usually inherited as a Mendelian dominant trait. However, in the large scale studies of Race[11] and Young and co-workers,[12] families were observed in which the blood of both parents of affected children could not be distinguished from normal by any available technique. Although spontaneous mutation is a possible explanation, in most such instances it is more likely that the expression of the abnormal gene was below the threshold of detection. Such "variable penetrance" is not uncommon, and a minimally affected parent may transmit a much more active form of the disease to offspring. It is also probable that HS, like many genetically determined diseases, is heterogeneous and not the result of a single mutant gene. Although unproved, the possibility of a recessively transmitted mutation could explain atypical cases. In deer mice a hemolytic disorder essentially identical to human HS occurs as an autosomal recessive trait.[13] Unequivocal homozygosity for HS thus far has not been shown, possibly, though not certainly, because the homozygous state may be lethal as suggested by Race.[11]

While earlier workers recognized that minor and major crises could punctuate the course of HS (See Dacie[14]), detailed studies by Owren[15] focused attention on their pathogenesis. In contrast to the generally held earlier opinion that such crises were hemolytic, it is now generally agreed that in major crises a temporary period of marrow aplasia is a far more common cause. In Owren's study,[15] four patients with crisis were members of the same family, supporting earlier reports (summarized by Dacie[14]) of "epidemic" familial crises. During the crisis (Figure 1), hemoglobin fell rapidly, severe reticulocytopenia intervened (0 to 0.3 percent), jaundice abated rather than increased, serum iron levels rose, granulocytopenia and thrombocytopenia occurred, and the bone marrow showed acute hypoplasia. Neutropenia and thrombocytopenia, however, are not always evident. Although the cause of the aplastic crisis (now widely recognized as occurring in a variety of chronic hemolytic states) is unclear, its occurrence at times in "epidemics" strongly supports an association with infection, probably most often of a viral nature. In normal subjects, hematopoiesis probably is also transiently depressed during certain infections, but

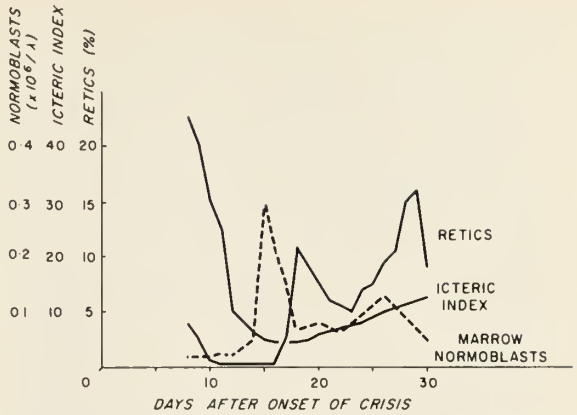

Figure 1.—The reticulocyte count (retics), icterus index, and numbers of marrow normoblasts in the days following onset of "aplastic crisis in a patient with hereditary spherocytosis." (Replotted from Owren's data.[15]) Note the early reticulocytopenia, diminution in numbers of normoblasts, and diminished icterus followed by reticulocytosis and sharp increase in marrow normoblasts.

(1) this is more severe in a marrow already laboring to compensate for hemolysis or (2) depression of production of blood cells is more serious and evident when accompanied by rapid peripheral destruction of erythrocytes. Aplastic crises are self-limited (usually 7 to 14 days). If examinations are not carried out sufficiently early, the resurgent marrow may appear cellular with an increase in young precursor cells. If the patient presents still later during recovery, reticulocytosis may obscure the fact that aplasia and reticulocytopenia were present earlier.

Although early students of the disease recognized its hemolytic origin, opinions as to its pathogenesis were varied. Chauffard[16] championed the possible etiologic role of hereditary syphilis and tuberculosis. Tileston's monograph[10] detailed the various theories held before 1922. These included postulated hemolysins, despite the fact that antibodies were not demonstrable. Others thought to implicate the hemolytic action of unsaturated fatty acids in serum. Tileston[10] more than 55 years ago concluded, however, that the spleen "is a necessary link for the production of other signs of the disease," and in some way "diminished resistance of the red cells is the leading factor in the causation of hemolytic jaundice" of the congenital type.

Although Naegeli[17] is usually credited with coining the term "spherocyte," its true origin according to Crosby[18] should be attributed to a monograph on blackwater fever published in 1908.[19] The authors, British Army officers as-

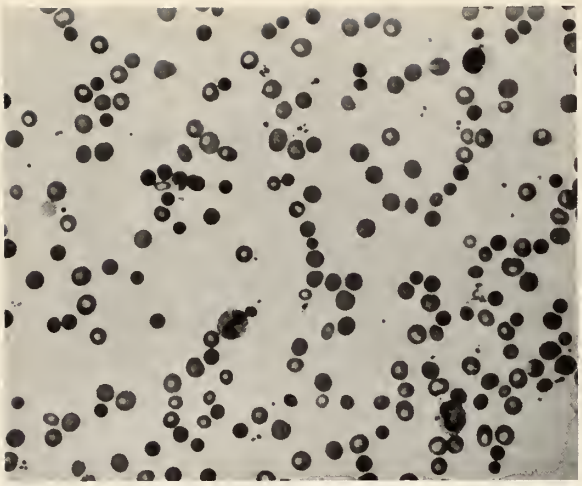

Figure 2.—Wright-stained peripheral blood film of a patient with hereditary spherocytosis. (Original magnification 400×.)

signed to India, carefully described the cell and proposed it be designated a "spherocyte." Naegeli, however, did invoke the erroneous dictum that the spherocyte was pathognomonic for hereditary spherocytosis, a concept invalidated many years later by Dameshek and Schwartz.[20] They showed that spherocytosis is a feature of certain acquired anemias, as well as of experimental anemias produced by antibodies.

In HS, the red cells are small (diameter 6.5 to 7μ instead of the normal 7.7 μ on stained blood films) but abnormally thick (2.2 to 4.7 μ with normal 1.95 μ).[22] Hence, they stain densely and lack the usual zone of central pallor (Figure 2). The increased thickness compensates for the decreased cell diameter, so that the mean corpuscular volume is usually normal or even increased. Haden[21] first clearly indicated the relationship of osmotic fragility to initial cell shape, pointing out that the osmotic fragilities of erythrocytes in a variety of human anemias, as well as in various mammalian species, depend on the ratios of their thickness to their diameters (the thickness index of Von Boros[22]). He succinctly stated the case as follows:

> The one fundamental variation from normal in congenital hemolytic icterus is the microspherocytosis. The anemia, jaundice, splenomegaly, reticulocytosis and increased fragility are all secondary to the globular form of the erythrocyte.[21]

Quantitative demonstration that osmotic fragility is indeed a function of shape was provided almost simultaneously by Castle and Daland[23] and by Ponder[24] in 1937. Soon thereafter it was found

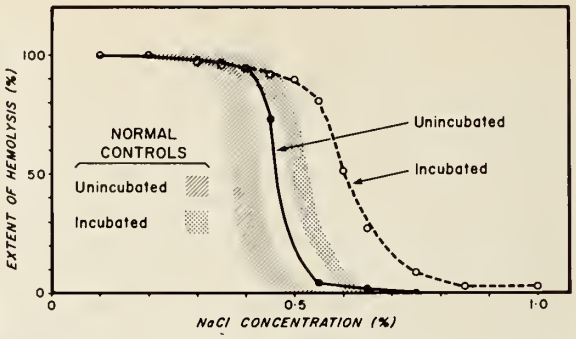

Figure 3.—The incubated (24 hours, 37°C) and unincubated erythrocyte osmotic fragility curves of a subject with hereditary spherocytosis compared with those of normal controls.

that the increased osmotic fragility of HS cells in fresh blood was accentuated by incubation for 24 hours at 37°C.[12,25] This became the basis of the more sensitive "incubated osmotic fragility test" often utilized in the diagnosis of cases with mild or doubtful abnormalities (Figure 3).

When normal human erythrocytes are incubated without added glucose, a series of metabolic events sequentially takes place. First, glucose and then 2,3-diphosphoglycerate levels fall and then adenosine triphosphate (ATP) depletion occurs. Initially, the erythrocyte, an osmometer[26] permitting the passage of water within milliseconds and the passage of anions such as Cl^- and HCO^-_3 only slightly more slowly, retains its relative impermeability to cations. Normally, K^+ and Na^+ slowly leave and enter the cell, respectively, moving "downhill" in accord with gradients resulting from the high intracellular concentration of K^+ and the high plasma concentration of Na^+. The correction of these movements requires active pumping of Na^+ to the outside and K^+ to the inside of the cell. This pumping requires a K^+-, Na^+- and Mg^{++}-dependent adenosine triphosphatase that is inhibitable by ouabain. A breakdown in the pump inevitably ensues when adenosine triphosphate is depleted secondary to glucose deprivation, and pump failure results in progressive loss of impermeability to cations.

The Pathophysiology of Hemolysis in Hereditary Sphirocytosis

In the early 1940's, Ham and Castle[27] and Dacie[28] studied the volume changes in normal and HS cells undergoing sterile incubation in the absence of added glucose (Figure 4). They found that during the first 24 hours, normal cells swell as a result of a somewhat greater net gain of Na^+

and water over K^+ loss. However, this is followed by cell shrinkage back to or even less than the original volume. Hemolysis does not occur during the period when the mean corpuscular volume is maximal, but only later when cell volumes are equivalent to or less than those present before incubation. As Selwyn and Dacie[29] commented, hemolysis under these conditions cannot be related solely to colloid osmotic lysis (although changes in cell cation and water content do occur) but must be due to some type of membrane "contraction" resulting in a decrease in the red cell surface-area/volume ratio. Hemolysis occurs when distention of the membrane ultrastructure permits the egress of first the metabolic intermediates and then the larger hemoglobin molecules. The sequence of events during such incubations is essentially the same for HS and normal cells *except that all changes are foreshortened and accelerated when HS cells are studied.*[27,28]

What, then, accounts for the accelerated changes observed with HS erythrocytes? First, HS erythrocytes are abnormally "leaky" and have an increased permeability to Na^+.[30-32] This propensity to accumulate sodium and water requires increased metabolism of glucose to man the pump and maintain cation homeostasis. This, in turn, implies greater dependence on glycolysis to regenerate adenosine triphosphate, an increased metabolic rate to sustain the extra effort of increased sodium pumping and greater sensitivity to glucose deprivation. Everything being equal, metabolic depletion of HS cells should be more rapid than that of similarly incubated normal erythrocytes. Second, metabolically depleted normal red cells do indeed physically lose membrane protein and lipids into the surrounding medium.[29,33-35] These occur without loss of hemoglobin and result in (1) an increase in the mean corpuscular hemoglobin concentration and (2) the attainment of a critical hemolytic volume through actual loss of effective surface area from the metabolically depleted red cells. Again, this "normal" process is substantially accelerated in HS cells. The membrane "contraction" prophesied by Selwyn and Dacie[29] is due, therefore, to membrane losses to which the HS cell is peculiarly susceptible.[33-35]

Considerable controversy has been generated as to whether increased cation permeability, or the increased susceptibility to membrane budding, is primary in causing the shortened red cell survival in HS. It has been pointed out,[36] for example,

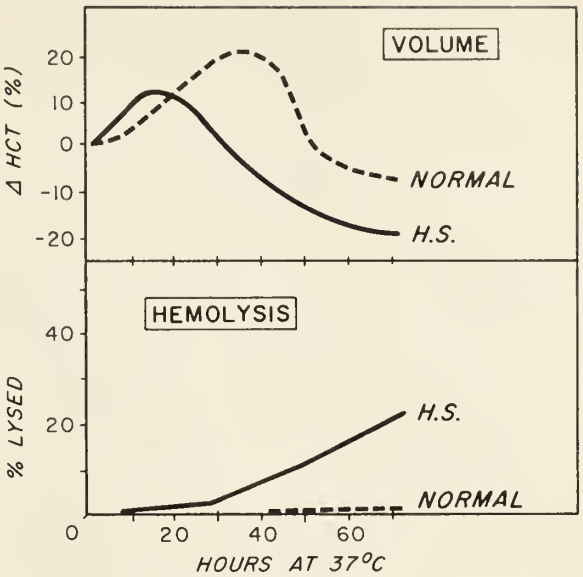

Figure 4.—Volume changes and time of hemolysis in normal and hereditary spherocytosis (HS) cells undergoing sterile incubation in absence of added glucose. (Redrawn from figure published by Weed[35]) Note that observed hemolysis does not correspond to period of maximal increase in red cell volume. The volume changes of HS cells are similar to those of normal erythrocytes but occur much earlier. HCT = hematocrit

that the diminution in osmotic fragility demonstrable in HS red cells of subjects rendered iron deficient by phlebotomy is not accompanied by improved cell survival, a fact suggesting that initial cell shape is not the only determinant of hemolysis. Wiley also reported that HS cells with the "leakiest" membranes paradoxically appear to survive the longest *in vivo*.[37] However, irrespective of the precise role of increased Na^+ flux and increased susceptibility of depleted cells to membrane loss in the pathogenesis of hemolysis, the fact remains that both properties represent departures from normal in the osmotically fragile hereditary spherocyte.

Normal cells that are metabolically depleted become less plastic and deformable, but freely circulating HS cells are already less deformable than normal. Jandl and co-workers[38] and later others[39,40] showed decreased filterability of HS cells *in vitro*. Leblond and associates[41] ingeniously measured the pressure required to deform the membrane or to pull an entire cell into a micropipette whose aperture diameter was smaller than that of the red cell. Hereditary spherocytes had notably reduced deformability, but this applied only to the mature cell. Marrow precusor cells and reticulocytes did not differ from normal by

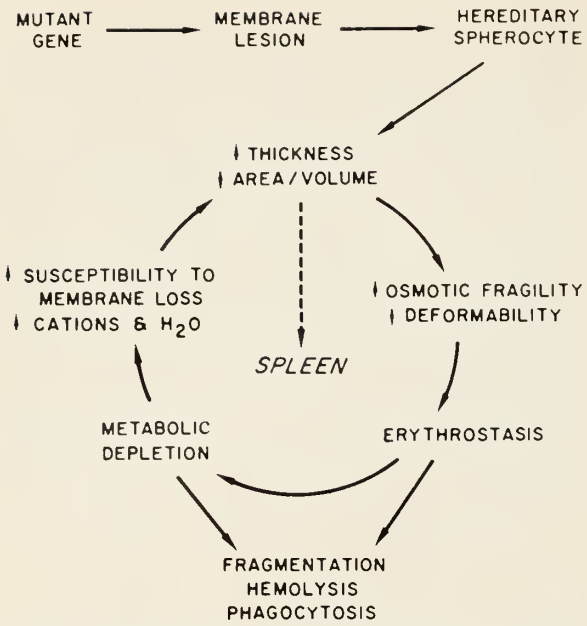

Figure 5.—Diagrammatic representation of the pathogenesis of hemolysis in patients with hereditary spherocytosis. The spleen provides a hostile environment where the hereditary spherocyte rapidly undergoes progressive changes resulting in its sequestration and destruction.

this technique. Normal red cell deformability has been shown to be highly dependent on adenosine triphosphate and magnesium levels and the maintenance of high adenosine triphosphate to calcium ratios.[42,43]

The mechanisms by which the spleen plays such an important role in producing the clinical manifestations of HS are closely related to the abnormal properties of the mature erythrocytes. The exact nature of circulation of blood through the spleen is still somewhat controversial. Normal red cells appear to traverse the spleen fairly rapidly, and the transillumination studies of Knisely[44-46] supported a "closed" type of circulation, that is, direct continuity between the terminal arterioles and the sinuses. Results of most other studies have supported the concept of an "open" circulation, with many arterioles emptying into the red pulp from which the erythrocytes must find their way back into the sinuses through small apertures in sinus basement membrane. Some of the dilemma of the "physiologically closed, morphologically open" enigma can be resolved if, as Weiss[47,48] suggested, the cordal spaces are regarded as partitioned to form a rather complete, if unconventional, vascular channel. Such a channel could conduct blood efficiently, much like an endothelial-lined vessel, from arterial terminations to apertures in the sinus wall. Recently, Barnhart and associates,[49,50] as a result of scanning electron microscopy studies on plastic corrosion casts prepared from human spleens, provided evidence of direct arteriovenous shunts and concluded that open and closed types of splenic circulation coexist in man.

Be that as it may, the spleen provides a potentially hostile and crowded microenvironment for red cells with defective deformability. The radial arteries in the white pulp give off branches at almost right angles, an anatomic feature resulting in skimming of plasma and fostering the later discharge of concentrated erythrocytes into the red pulp or cordal region. Emerging from here, the red cell (diameter 7 to 8 μ) must traverse apertures in the sinus wall estimated as averaging only 3 μ in diameter. In addition, the high endothelium of the smallest splenic arterioles may result in arteriolar apertures sufficiently small as to retard poorly deformable erythrocytes. The splenic test may extend to the sinus itself, where contraction of the terminal end has been observed to result in retention of blood in the sinus lumen for some time.[45]

The remarkably pliant normal red cell can pass these tests relatively easily, whereas the less pliant HS cells undergo erythrostasis in an almost pasty red cell mass in which glucose is locally depleted, acid metabolites accumulate, and actively metabolizing, phagocytic macrophages abound. Abnormally sensitive to glucose deprivation, abnormally disposed to further membrane losses by budding and lacking in normal deformability, the HS cell undergoes progressive changes leading to its ultimate destruction (Figure 5).

Emerson and colleagues[25] first transfused serologically identifiable normal donor erythrocytes into recipients with HS scheduled for splenectomy. Studies on the removed spleen showed selective trapping of HS cells, and these were osmotically more fragile than the freely circulating red cells of the patient. Young and associates[51,52] confirmed that removed spleens from subjects with HS had trapped the most abnormal erythrocytes. Further, *in vitro* perfusion of mixtures of HS and normal red cells into spleens removed from patients with idiopathic thrombocytopenic purpura established that these spleens also selectively removed the HS cells. Subsequent investigations[53,54] with labeled HS erythrocytes have abundantly confirmed their increased propensity to stagnate in the microenvironment of the spleen, where the trapped cells

undergo a "conditioning" process. Although initially they may escape back into the general circulation, with each sojourn in an environment predisposed to metabolic depletion there is progressive loss of membrane, progressively less deformability, and the assumption of a progressively more spherocytic shape. After several passages, the spherocyte is no longer able to traverse the tiny apertures leading back into the sinuses, fragments, and undergoes phagocytosis. "Conditioned" cells that have succeeded in escaping a few passages through the splenic circulation account for the most osmotically fragile "tail" characteristically seen on the osmotic fragility curve in hereditary spherocytosis.

The Cellular Defect of Hereditary Spherocytosis

What is the actual inherited molecular lesion that represents the ultimate pathogenesis of HS? A variety of abnormal properties of HS red cells have been defined, but none has been identified as the fundamental defect. The two most frequently proposed postulates emphasize an abnormality of the red cell membrane but do not specify its nature. As discussed earlier, the first of these emphasizes the predisposition to enhanced membrane loss resulting in reduction of the critical hemolytic volume.[55] The second stresses increased permeability to cations, an increase in energy metabolism required by an increased rate of active cation transport and colloid osmotic lysis as the hemolytic mechanism.[31,56] Extensive studies of glycolysis in HS compared with normal red cells have included measurements of anaerobic glycolytic and oxidative hexose-monophosphate pathway enzymes, glycolytic intermediates and flux of inorganic P_i into adenosine triphosphate[32] and other phosphorylated intermediates of glycolysis.[57] Although an occasional study has reported abnormalities, the weight of evidence suggests that no specific abnormality in glycolysis, in the pattern of glycolytic intermediates, or in the flux of P_i into adenosine triphosphate and other phosphorylated compounds exists in HS erythrocytes.

Although total lipids have been reported to be somewhat decreased both before[33,58] and after[35] splenectomy and abnormalities of phospholipid turnover have been suggested,[59] no consistently demonstrable data support specific abnormalities in membrane lipid structure. Phospholipids such as sphingomyelin, phosphotidylcholine and phosphotidylserine are reported to lack long chain fatty acid conjugates (acids with more than 20 carbon atoms), and a reduced capacity of HS membranes for lengthening lipid chains has therefore been postulated.[60] Although mature red cells cannot synthesize fatty acids, membrane surface area can be increased and osmotic fragility reduced by media rich in cholesterol or linolenoyl sorbitol.[61] Intact HS red cells, as well as their ghost membranes and liposomes prepared from their lipid extract, exhibit increased microviscosity, and this is reported to correlate with the clinical severity of the disorder.[62,63] Although a role of altered membrane lipids in the pathogenesis of HS remains possible, evidence does not substantiate that observed abnormalities are primary, rather than secondary to the underlying lesion responsible for the morphologic and osmotic abnormalities of the red cell seen even in patients in whom splenectomy has been carried out.

Recently, study has focused most frequently on membrane proteins. Lipid-free proteins extracted from HS membranes at low ionic strength resist aggregation when the ionic strength and divalent cation content are increased in comparison with those derived from normal cell membranes. Defective formation of microfilaments in HS cells has been postulated as an explanation.[64] Vinblastine at concentrations far higher than those attained when the agent is used therapeutically induces spherocytosis in intact cells and precipitates less protein from HS than normal membranes.[65] Vinblastine is known to interfere with microfilament formation in a variety of cells. Agglutination of HS red cells washed in electrolyte-free media is reversed only by considerably higher concentrations of added Ca^{++} than those required for normal erythrocytes.[64] Even in normal red cells,[42] deformability is altered by changes in the distribution of Ca^{++}, and relative deficiency of a Ca^{++}-dependent adenosine triphosphatase has been reported in HS.[66] However, the intramembrane distribution of Ca^{++} is not readily ascertained, nor are possible alterations in membrane Ca^{++} or Ca^{++}-dependent reactions separable into primary or secondary events in HS. Finally, a relationship of abnormally arranged membrane sulfhydryl groups to sphericity is suggested by the fact that agents binding these groups produce sphering of normal erythrocytes. Cells so modified possess a number of properties mimicking those of the hereditary spherocyte.[67]

Within the past year, several investigations have addressed the concept that altered membrane

protein phosphorylation may be pathogenetic in HS.[68-70] That an abnormal state of microfilamentous membrane proteins having contractile properties may be at fault in HS is inherently attractive and has been rendered more so by the demonstration that such a protein, membrane spectrin, is a major substrate for phosphorylation by erythrocyte protein kinase. Spectrin is a complex of two peptides and may exist in several aggregation states.[71] It resembles myosin (but with some differences), and *in vivo* it exists as a complex with erythrocyte actin. It interacts with both lipid bilayers and with intrinsic membrane proteins of the red cell, binds Ca^{++} and adenosine triphosphate, has distinguishable weak Mg^{++} and Ca^{++} adenosine triphosphatase components, and is phosphorylated by adenosine triphosphate in the presence of protein kinase.[71] There is evidence that it may play a major role in controlling membrane deformability. Spectrin comprises 20 to 25 percent of the membrane protein, and removal of spectrin from ghosts (red cells without hemoglobin) causes them to break into vesicles. Spectrin is greatly alterable by changes in distribution and amount of red cell Ca^{++}, and normal membrane deformability is maintained only when the cell interior is essentially Ca^{++}-free. In addition, genetically determined HS in mice has been reported to be associated with a severe deficiency of erythrocyte spectrin.[72] In short, the search for a defect in the state or function of human erythrocyte spectrin in HS offers an attractive avenue of exploration.

Several studies are in agreement that spectrin is the major membrane protein phosphorylated by membrane kinases. Unfortunately, there is little agreement in other respects. Defective phosphorylation of spectrin and of the cyclic adenosine monophosphate-dependent phosphorylation of another membrane protein have been reported by Greenquist and Shohet[68] in 22 of 25 patients with HS. Beutler and associates[70] concurred with modest diminution in membrane protein phosphorylation of HS cells after 60-minute assays utilizing membrane suspensions. However, the phosphorylation reaction was linear only for short periods, and during the period of linearity HS and normal cells behaved similarly. In contrast, Matsumoto and co-workers[69] found diminished spectrin phosphorylation, uninfluenced by previous splenectomy, in HS cells during the nearly linear first ten minutes of incubation. In further support of a role for spectrin, membrane phosphorylation was strongly inhibited at the temperature (48° to 50°C) at which spectrin "melts" in a calorimeter.[69] Also, red cell sphering began on exposure to concentrations of the sulfhydryl-binding agent, N-ethylmaleimide, which produced similarly decreased membrane phosphorylation in red cell ghosts.

The observations are provocative, but a final decision regarding the role of membrane protein phosphorylation in the pathogenesis of HS in man must be deferred. The assay system is very complex,[68-70,73-75] and the exact form of the spectrin-actin complex is a complicated function of the ionic strength, status of membrane proteins in the assay material, method of preparation, temperature, time, and distribution and concentrations of divalent cations.[71-75] The number of protein kinases potentially involved is unknown. The association of regulator and catalytic subunits in protein kinase is conditioned by a variety of factors, and free and complexed forms of catalytic subunits may even differ radically in their substrate specificity.[75] Parallelisms between the effects of heat and sulfhydryl-binding agents on the protein kinase system on the one hand and their ability to produce sphering on the other are complicated by the generalized potential for cellular damage inherent in heating or interfering with ubiquitously distributed sulfhydryl groups of protein. In addition, analogous or even more severe diminutions in membrane-phosphorylating activity than those reported in HS have been described in four cases of hemoglobin sickle cell disease[70] and in hereditary stomatocytosis.[76] The problem at the moment derives in large part from the inability to know experimentally the spatial relations and composition of enzymes, substrates, cofactors, and divalent cations in highly organized membrane preparations. It is hoped that the discovery of a molecular lesion in HS will evolve from the present base of knowledge, but this happy day has yet to arrive.[77]

Diagnosis of Hereditary Spherocytosis

The diagnosis of HS is usually not difficult. The presence of large numbers of small round densely staining spherocytes on the stained blood film normally reflects either HS or acquired Coombs-positive autoimmune hemolytic anemia associated with warm agglutinins. A negative Coombs test in the first instance and a positive test in the second most often serve to establish the correct diagnosis. Confirmation of the spherocytic nature

of the erythrocytes is usually readily achieved by means of the osmotic fragility test done on fresh and incubated blood. The increased susceptibility of HS cells to lysis under conditions of glucose deprivation is easily demonstrable by the autohemolysis test of Selwyn and Dacie.[28] When normal blood is incubated sterilely and without glucose additives for 48 hours, only minimal hemolysis occurs. When HS blood is similarly incubated, autohemolysis is usually well marked but correctable by glucose additives. Labeling an aliquot of patient cells with chromium 51 and subsequently showing their abnormal sequestration in the spleen by external body counting confirms the phenomenon of splenic erythrostasis, but this is not usually necessary. Further, in many but not all cases of HS, the history of jaundice and anemia from an early age and a family history of early gallstones, jaundice, anemia, splenomegaly and perhaps splenectomy point to its hereditary nature. Normally, this is readily confirmed by family studies that show other affected members and Mendelian dominant transmission.

Diagnosis is more difficult in patients with mild abnormalities or when the disorder is not demonstrable in either parent. In the former, differential diagnosis lies chiefly between HS and a wide variety of so-called "nonspherocytic" hereditary hemolytic syndromes such as those associated with certain erythrocyte enzyme deficiency states.

Treatment of Hereditary Spherocytosis

The treatment of HS is splenectomy with the possible exception of fully compensated, very mild cases lacking jaundice, anemia or a history of crises. Even in such cases there is room for argument, because amelioration of mild compensated, but chronic and life-long hemolysis provides some protection against the development of gallstones. The first successful splenectomy was apparently carried out in 1887 by Wells who, operating with the erroneous diagnosis of abdominal tumor, found instead an enlarged spleen.[78] Although Wells was unaware of the true diagnosis, Dawson 40 years later restudied the patient and found the characteristically increased osmotic fragility of the red cells in an otherwise healthy patient.[78] Wells had done the first splenectomy in England in 1865 and the second and third in 1868 and 1875—all with fatal outcomes. Dawson[78] in the Hume Lectures expressed some wonder at the surgeon's temerity in attempting a fourth and some admiration at the operative skill that permitted survival under conditions that did not include asepsis during the procedure. Micheli in 1911[79] successfully removed the spleen in a patient with the acquired type, and the fortunately brilliant result soon led to widespread use of the procedure with almost complete success in the congenital form of the disease.

Splenectomy in HS has limited hazards.[80-82] Patients less than 4 to 5 years of age have an increased risk of infection, particularly pneumococcal sepsis, after splenectomy. For this reason, if at all possible the operation should be postponed until the patient is 5 years old. In adults who have had posttraumatic splenectomy, statistical evidence of some slight but significant increase in predisposition to infection has been adduced, and it is said that this is slightly greater in patients with HS.[81] However, the risk of serious sepsis is very low. Schilling[82] failed to identify a single instance of fatal bacterial infection in a recent retrospective study of 61 subjects with HS (with collectively 800 patient-years after splenectomy). Furthermore, admission to hospital was no more frequent in patients after splenectomy than in normal control subjects. Although splenectomy eliminates anemia and prevents further aplastic crises, its greatest reward is the reduced incidence of complicating cholelithiasis and cholecystitis. Patients with HS in whom splenectomy has not been done should receive folate supplementation daily, a measure that most investigators agree lessens the likelihood of aplastic crises. It should also be mentioned that chronic leg ulcers without obvious underlying vascular causes usually clear after splenectomy in HS patients.[83]

Occasionally, removal of the spleen is not followed by the usual complete clinical recovery. This has often been attributed to failure to remove accessory spleens or to seeding of the peritoneum by splenic tissue at the time of operation. Cases in which this explanation has been proved are exceedingly rare[84] and are convincing only if prompt "cure" results from removal of remaining splenic tissue. Brook and Tanaka[85] and also the author have seen cases in which reticulocytosis and jaundice persisted after splenectomy in patients with classic HS who had concomitant heterozygosity for pyruvate kinase deficiency. The speculative possibility exists that associated abnormalities in the glycolytic machinery that are too mild to have clinical manifestations in nor-

mal subjects might result in some diminished survival of the postsplenectomy HS cell with its greater dependence on glycolysis.

After splenectomy, certain events normally occur.[14] The patient's hemogram returns to normal and remains so. Haptoglobin levels return nearly to normal levels.[82] Microspherocytosis persists although often in a less flagrant form because of the absence of the most spherocytic "splenic-conditioned" cells. By the same token, osmotic fragility continues to be increased, but the "tail" of most osmotically fragile cells (presumably those with previous passages through the spleen) often disappears from the osmotic fragility curve. Jaundice normally disappears as does significant reticulocytosis, although sensitive measurement of red cell life span indicates that survival is slightly below normal.[86] The autohemolysis test also remains abnormal, but in some instances may show improvement in the degree of observed hemolysis.

It may be concluded that while much is known about the small, osmotically fragile, densely staining spherocyte, the definitive documentation of the responsible molecular lesion still remains an elusive goal.

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Important Advances in Clinical Medicine

Epitomes of Progress — Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in pathology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Effects of Exercise on Enzyme Interpretation

CHANGES IN serum enzyme activity after exercise depend on the magnitude of activity, physical condition of the subject and the specific characteristics of the enzyme, although heat stress and hemolysis associated with exercise also could play a role. Serum enzyme of clinical importance that may change with exercise include glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), adenylic kinase (AK), lactic dehydrogenase (LDH), creatine kinase (CK). The effects of exercise, including endurance training, on LDH and CK are of particular interest since changes in their serum activities occur in cardiac disease. With endurance exercise training, the rise in LDH activity seen immediately after exercise disappears. Decrease in serum LDH activity immediately after exercise in conditioned men may be due to more rapid clearance of LDH from the serum as a result of increased cardiac output and organ blood flow accompanying endurance exercise. However, if the severity of exercise exceeds the usual training level then the rise in total serum LDH still may occur.

Experimental findings suggest that serum CK activity is the most sensitive index of acute exercise stress. With continued physical activity in trained men CK levels remain elevated. Similar findings in untrained persons have been reported. Hospital patients at bed rest had CK levels that were significantly lower than ambulatory, sedentary outpatients. Since CK levels are frequently used to diagnose pathologic conditions it is particularly critical that the subject's physical activity level be taken into account to avoid an incorrect diagnosis. For example, serum CK levels in endurance-trained men on some exercise days would be within ranges considered abnormal if the factor of continuous training were not considered. Appropriate caution, therefore, should be used in making critical judgments from the enzyme assays in trained subjects.

GOT and GPT levels also may be affected by exercise in man but in trained persons their levels are usually unchanged. Serum AK levels are ele-

vated after exercise stress. Interestingly, in endurance trained persons, resting serum AK levels are three times greater than those observed in untrained, normal, healthy men. This disparity between different enzyme activities suggests that (1) selective enzyme trends may occur across cell membranes; (2) the different enzymes may have different appearance times after stress; (3) changes in regional blood flow distribution may be responsible, and (4) the different enzyme activities may reflect differences in tissue concentrations.

Of the various enzymes assayed from human sera, CK is the most sensitive index of the degree of acute exercise stress imposed on a person. Therefore, when one interprets isolated serum CK levels it is important to consider the level of physical activity to avoid an incorrect diagnosis. Appropriate caution should be used in making clinical judgments from these enzyme assays in well-conditioned persons.

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Wolfson S, Rose LI, Bousser JE, et al: Serum enzyme levels during exercise in patients with coronary heart disease: Effects of training. Am Heart J 84:478-483, Oct 1972

Therapeutic Drug Monitoring

CONTROLLING DRUG THERAPY recently has become a primary focus for clinical laboratories. There are three major ways in which the resources of a laboratory are useful to a clinician seeking a specific treatment objective: (1) measurement of drug levels in the blood, (2) measurement of body functions which modify the disposition or response to drugs and (3) application of multivariate analysis for dose planning.

Measurements of drug levels in blood are of primary importance in the control of drug therapy. For drugs with low therapeutic indices (such as digoxin and gentamicin), monitoring of the blood level is necessary to compensate for interindividual variability and maximize the benefit/risk ratio for each individual patient. In other clinical settings, serum assay is occasioned by failure of a patient to respond in the anticipated way. If the drug assay shows little or no drug in the blood then considerations include: noncompliance, bioavailability problems, malabsorption and inappropriate dosage forms. If adequate serum levels of the drug are found, in the face of no response, then a diagnostic error should be considered (that is, the patient does not have a condition which responds to the agent prescribed). Other settings in which serum drug levels are important include documenting the particular serum level associated with control of seizure disorders and control of the rescue process when high dose methotrexate therapy with citrovorum factor rescue is used.

Assessment of specific body functions that modify the disposition of and response to specific drugs is a major area of laboratory responsibility. Assessment of creatinine clearance is important when drugs eliminated by glomerular filtration are involved. Hepatic status can be evaluated, thereby precluding overdosage in patients with defective hepatic function when drugs metabolized primarily by this organ are used. Functional interaction between drugs also can be assessed by laboratory monitoring. Occasionally, clinicians can encounter accelerated hepatic metabolism of one drug (for example, crystaline sodium warfarin [Coumadin®]) due to hepatic enzyme induction by a second drug (for example, phenobarbital). By careful laboratory monitoring this functional drug interaction can be assessed.

Dose planning for some drugs requires the simultaneous evaluation of multiple variables (multivariate analysis). For example, to plan a digoxin dosage schedule requires the simultaneous evaluation of multiple measures: target tissue levels, height and weight (to calculate lean body mass); serum creatinine, urine creatinine and 24-hour urine volumes (to calculate creatinine clearance); serum potassium and oxygen pressure (to establish toxicity risk). Computations of this complexity are greatly facilitated by computer programs such as those developed by Jelliffe and co-workers for cardiac glycosides. Additional programs have become available for use with the aminoglycoside antibiotics, lidocaine and procainamide. In regard to digoxin toxicity, at least two separate studies have documented improvement in patient care with reduction in digitalis toxicity using computer assisted dosage regimens.

Utilizing all of these resources, a laboratory can provide clinicians with a report containing the dosage plan for a particular patient. The report should contain a recommended dosage schedule, an estimate of the toxicity risk together with a

predicted serum level at some appropriate time which will serve as a "check point" for the dosing plan. Significant deviation from the predicted level would indicate the need for further evaluation and possible revision of the dosage plan.

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HLA in Paternity Testing

HISTOCOMPATIBILITY ANTIGEN (HLA) typing now is recognized throughout the world as the single most discriminating test for determination of nonpaternity. Because of the large number of antigens involved in one genetic system of closely linked loci and the scattered distribution of these antigens in the population, the chance of exclusion with HLA typing alone is at least 91 percent and is 95 percent in combination with ABO and Rh typing. HLA testing has been used for about five years in paternity cases in Europe, and recently a joint committee of the American Medical Association and the American Bar Association studying serologic tests for paternity evaluation recommended "widespread inclusion of HLA studies in the battery of tests used in cases of disputed paternity."

HLA is the major histocompatibility system in man, and has an extreme diversity of antigens in several closely linked serologically detectable genetic loci. At present, the practical use of HLA in paternity cases is confined to typing of two loci, HLA-A and HLA-B. The system is one of codominant genes, so two antigens may be present for each locus. The World Health Organization Leukocyte Nomenclature Committee recognizes a total of 39 separate specificities for the A and B loci. A tissue typing laboratory that can detect most or all of these specificities can type for about 300 haplotypes with as many as 100,000 genotypes.

In cases of nonexclusion of a putative father, an estimate of the likelihood of paternity is desirable in utilizing the serologic results. In "one-man" cases, generally a computation is used that compares the nonexcluded putative father with a random male in the population. In our laboratory, formulas have been derived to utilize population haplotype frequencies rather than simple gene frequencies, since haplotypes generally are inherited as a unit and genetic disequilibrium is known to exist between antigens of HLA-A and HLA-B. This computation does not assume probable haplotypes, but takes into account all possibilities for each person as well as considering recombination frequencies. In our experience with over 1,000 disputed paternity cases, nearly 90 percent of the nonexcluded cases had probability of paternity greater than 90 percent. Undoubtedly, utilization of HLA typing in paternity cases in the United States will continue to increase rapidly as education about the extreme usefulness of such tests becomes more widespread and legislation is altered accordingly.

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Pacemaker Postmortem

THE CARDIAC PACEMAKER stands in the forefront of the bionic age. Thousands of people now live and eventually will die with a complex electrical pulse generator functioning inside their bodies. This generator provides a substitute electrical impulse for the heart's completely or incompletely blocked electrical system. In death, the question sometimes arises whether a pacemaker malfunction or complication contributed in any way.

The pathologist, therefore, should examine the pacemaker and its lead as an integral part of an autopsy. He or she always should ask: (1) Was there a signal? (2) Was it effective? (3) Could anything have altered it?

The generator should be tested electronically for rate, pulse amplitude, pulse width and R-wave

inhibition. Any hospital where pacemakers are implanted should have a device that can test for these. The lead should be inspected *in situ* before removal to make sure it is in the proper location and is providing a proper myocardial contact. Testing at the lead terminal will establish its continuity with the generator.

The history is important to determine if some outside electrical exposure such as electrocautery could have affected the unit.

The presence of the pacemaker as a foreign body can complicate matters. The implant site can become infected and the infection may migrate down the lead into the circulatory system. Thrombi may form about the lead and provide a source of emboli.

Testing of cardiac pacemakers postmortem not only aids in determining the cause of death but also, on a larger scale, helps prevent other deaths by monitoring for product defects. These should be reported to the Bureau of Medical Devices, Food and Drug Administration.

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Platelet Function Testing

PLATELETS occupy a key role in maintaining vascular integrity and initiating the clotting process. In recent years increasing interest has developed in testing quantitative as well as functional variations of platelets.

Although the reference method for platelet counting is phase microscopy, a number of reliable automatic counting devices are available. Only rarely is a factitious result produced by cold agglutinins, platelet satellitosis or giant forms of platelets.

The bleeding time is the classic measure of platelet effectiveness because it is sensitive both to quantitative and qualitative alterations.

The Ivy bleeding time test is done by inflating a sphygmomanometer cuff to 40 mm of mercury, making an incision lower on the arm and determining the duration of bleeding (normal 2½ to 10 minutes). Standardization of this procedure has been improved with a template which controls the length and depth of incision. Times are prolonged in thrombocytopenia, usually in von Willebrand disease and often in normal subjects taking aspirin.

Platelet retention testing involves passing blood through a column containing glass beads. Normally 80 percent of platelets are retained in the filter bed. This test is more sensitive than the bleeding time test but subject to many variables. It would be more useful if a standardized commercially available kit allowed greater interlaboratory comparison.

Clot retraction measurements are semiquantitative appraisals of platelet function. Retraction is deficient in thrombocytopenia and in a rare autosomal recessive disorder, Glanzmann thrombasthenia. Careful laboratory control is important.

Platelet aggregometry is done by passing a beam of light through a suspension of citrated platelet rich plasma. On addition of appropriate reagents an aggregate forms, causing a change of light transmission. Adenosine diphosphate (ADP) can aggregate platelets directly. Epinephrine and collagen produce a biphasic curve of aggregation by inducing platelet secretion and release of endogenous ADP.

A series of defects in primary and secondary aggregation has been noted in patients with bleeding disorders. Patients with von Willebrand disease show impaired, ristocetin-induced platelet aggregation. In thrombasthenia, platelets do not aggregate when exposed to ADP. The best known acquired functional alteration is that produced by aspirin. Since many aspirin derivatives and other drugs affect platelet aggregation, all medication should be avoided for ten days before the test is done. With platelet counts below 50,000 results of aggregometry are unreliable.

A dialysable substance present in the blood of uremic patients interferes with platelet aggregation. In a patient with cirrhosis there also may be defective platelet function.

Tests of platelet functions are influenced by many variables and can be capricious. Thus laboratory standardization of equipment, sampling technique and normal controls is particularly important.

Platelet aggregometry is sensitive to so many agents that it seems prudent to show an observed abnormality on more than one occasion before assigning it a causal role in a patient with a bleeding history. Additional clinical experience

is needed to evaluate the significance of an abnormal result when the test is done before surgical operation. It has merit when considered along with history of previous response to trauma and the bleeding time.

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Common Neoplasms of Pet Animals

SINCE JULY 1963 a survey of the incidence of various neoplasms of pets has been conducted by the Animal Neoplasm Registry of Alameda and Contra Costa Counties, under the direction of Robert Schneider, DVM. The physical location of the registry is the School of Veterinary Medicine, University of California, Davis. All veterinarians in the two counties have been invited to submit biopsy or autopsy specimens from animals suspected of having neoplastic disease, and statistics are available on over 40,000 animals.

Comparison of cancer incidence rates adjusted to the same population age distribution for human beings, dogs and cats indicates rates per 100,000 individuals of 300.3, 213.0 and 264.3, respectively. Sites with high malignant rates in man not shared with dogs and cats are digestive tract, lung, uterus, and prostate. A site with high rates in all three species is the female breast. Female dogs are especially prone to mixed epithelial and stromal mammary tumors, the great majority of which are benign.

Some tumors of animals are not recognized in human beings and others have unusual characteristics when they occur in animal hosts. For instance, the frequent histiocytoma of canine skin is a benign self-limited lesion peculiar to young dogs, occurring as a firm nodule or "button" up to 1 cm in diameter, and made up of monotonous cells of reticuloendothelial origin.

Sertoli cell tumors of the testis are extremely common in dogs and rare in human beings. They produce a feminization syndrome marked by loss of hair and the attraction of other male dogs as if they were females in heat. Angiosarcomas and cutaneous mast cell tumors are also frequently found in dogs and are unusual in humans.

Cats and human beings have similar tumor site predilection, but the incidence of lymphomas in cats is extremely high. Lymphomatous diseases of cats are believed to be due to viral infections, and clusters of feline tumors are common. Attempts have been made to relate the feline neoplasms to lymphoid tumors of human beings, but specific studies for the purpose do not support such a relationship.

The principal tumor of female rats is fibroadenoma, a bulky neoplasm common in mammary glands of aging animals. The principal "tumor" of horses is equine sarcoid, a fibromatosis of the skin which appears as cellular collagenous tissue forming a localized dermal mass.

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Hemopoietic Dysplasia (Preleukemia)

ELDERLY PATIENTS who clinically have a moderately severe refractory anemia with quantitative and qualitative abnormalities of erythropoiesis, granulocytopoiesis and megakaryocytopoiesis, with or without chromosomal abnormalities, may have hemopoietic dysplasia (HD). In an estimated 70 percent of such patients overt acute myelogenous leukemia (AML) develops within two years, hence the designation of preleukemia. The term should be avoided since many patients live for years and 10 percent recover completely (Personal communication from R. W. Pierre). (So far none of these have had karyotypic abnormalities. Conversely, karyotypic abnormalities do not presage an early leukemic conversion.) HD is comparable to cervical dysplasia in that it is precancerous in some, but not all cases. Dysmyelopoietic syndromes, myeloid dysplasia, refractory anemia with excess myeloblasts (promyelocytes in American terminology) are synonyms. Chemotherapy appears contraindicated, though treatment with cortisone has been found helpful in correcting peripheral cytopenias.

Morphologic features helpful in diagnosis are

erythroid hyperplasia with normal or low peripheral reticulocyte count; megaloblastic changes unresponsive to B_{12} or folic acid; ringed sideroblasts; bizarre erythroid maturation; megakaryocytes with one or two small, round nuclei and mature granular cytoplasm (if representing 25 percent of all megakaryocytes); giant platelets; platelets with granules; a left shift toward promyelocytes, and abnormalities of granulocytic maturation, including pelgeroid forms. At least two cell lines should be affected, each showing one or more of the mentioned abnormalities to establish the diagnosis of HD with confidence.

The correct diagnosis is important so that chemotherapy will be given promptly to patients with AML and withheld from those with HD. The distinction between the two identities is readily made by any competent hemotologist or pathologist familiar with the diagnostic criteria for AML. Referral of HD to centers participating in a registry of HD now being organized should eventually allow us to separate patients with "true preleukemia" from those who will progress to spontaneous cure and an intermediate group with a prolonged course of indeterminate duration.

At present there are no criteria available to predict the outcome in individual cases.

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Current Status of Tests for Antinuclear Antibodies (ANA) in Rheumatic Diseases

ANTINUCLEAR ANTIBODIES (ANA) are present in the sera of many patients with systemic rheumatic diseases. The important specific antibodies to nuclear antigens are listed in Table 1.

The recommended tests for screening of patients' sera for ANA are the indirect immunofluorescent or immunoenzyme tests using rat or mouse kidney substrate tissue. The immunofluorescent test should involve a titering of positive cases with a description of nuclear staining patterns. Nuclear rim staining can be obtained with antibodies to double-stranded deoxyribonucleic acid (DNA) or to deoxyribonucleoprotein. Antibodies producing the speckled pattern of staining are those reacting with several nuclear protein antigens.

TABLE 1.—*Immunological Specificities of Antinuclear Antibodies*

Antibodies to deoxyribonucleic acid (DNA)
Reactive only with double-stranded DNA
Reactive with double and single-stranded DNA
Reactive with single-stranded DNA
Antibodies to deoxyribonucleoprotein (DNA-histone complex)
Antibodies to histones
Antibodies to nonhistone protein
Sm antigen (glycoprotein)
Ribonucleoprotein (RNP, ribonucleic acid (RNA)-protein complex)
SS-A (recognized by sera from Sjögren syndrome, chemical nature unknown)
SS-B (recognized by sera from Sjögren syndrome, chemical nature unknown)
Scl-1 (recognized by sera from scleroderma, chemical nature unknown)
Antibodies to nucleolar RNA (4-5S nucleolar RNA)

One must use other immunological tests besides an indirect immunofluorescent test to precisely identify the immunological specificities of ANA. The recommended test for antibodies to DNA is the radioimmunoassay procedure. Antibodies to DNA are present in many systemic rheumatic diseases and patients with systemic lupus erythematosus (SLE) usually have higher concentrations of DNA antibodies. Antibodies to Sm antigen and ribonucleoprotein (RNP) have been detected by passive hemagglutination, immunodiffusion and electroimmunodiffusion tests. Antibodies to Sm antigens have been shown to be highly specific for SLE and may be a serological marker for SLE. Antibodies to nuclear RNP have been found in several systemic rheumatic diseases; however, in patients with mixed connective tissue disease (MCTD), extremely high titers of RNP antibodies are seen.

More recently, an immunodiffusion test with antigens extracted from Wil_2 (a human lymphoblastoid tissue culture cell line) showed Sjögren syndrome has antibodies reacting with other nonhistone proteins.

In summary, one should use the indirect immunofluorescent screening test which will detect the presence of all types of ANA. Once the presence of ANA is noted, every effort should be made to identify the precise immunological specificity of

the ANA. Specific identification of ANA will aid in the differential diagnosis and management of the disease.

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Alloimmune Neonatal Thrombocytopenia

ALLOIMMUNE neonatal thrombocytopenia (ANT) is an uncommonly reported disease. It is recognized in about one per 5,000 births, but it probably occurs much more frequently. ANT is analogous to Rh hemolytic disease of the newborn, except that the transplacentally acquired maternal antibody is directed against paternal antigens on the fetal platelets rather than on red cells. Usually the Pl^{A1} platelet antigen, present in 98 percent of the population, is involved.

The first-born infant has been affected in about half the reported cases. While petechiae, ecchymoses and purpura may appear at birth, more often these will develop several hours later. The platelet count is usually less than 30,000 per cu mm. The most serious threat to the infant is intracranial hemorrhage with possible neurologic injury or death.

Specific diagnosis of ANT is made difficult by the general unavailability and limited reliability of platelet antibody testing. Treatment can rarely await the establishment of the specific diagnosis, but must be instituted on the basis of a diagnosis of exclusion of other (and there are many) possible causes of neonatal thrombocytopenia.

Exchange transfusion to wash out the offending antibody has been tried with limited success. (The IgG antibody has about a 45 percent/55 percent intravascular/extravascular distribution and a half-life of 23 days.) The best therapy is probably transfusion with platelets lacking the Pl^{A1} antigen. Such platelets will be found in only 2 percent of the general population and platelet typing is not commonly available. The mother's platelets, however, will be compatible as she will lack the antigen against which she has formed the antibody (this will be true regardless of the antigen specificity).

It is essential that the maternal plasma be removed from the platelet preparation since maternal plasma is the source of the offending antibodies. The platelets can be suspended for infusion in group AB donor plasma.

With early diagnosis and appropriate therapy there should be rapid hematologic improvement. Occasional patients may require a second infusion of maternal platelets. Without treatment a mortality rate of about 14 percent has been reported in the literature.

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Amyloid Fibrils in Urine

AMYLOIDOSIS is a connective tissue disease, first described by Virchow, in which deposits of a hyaline protein carbohydrate material are laid down between the parenchymal cells of various organs, gradually infiltrating them and preventing their normal function. Blood vessel walls are especially susceptible to amyloid and it is in these areas that it can initially be seen in histological sections.

For diagnosis, a rectal biopsy can be done in the operating room, or a renal biopsy may be done using fluoroscopy. However, both of these procedures involve patient discomfort and major operating room costs. Such invasive procedures run the risk of serious internal bleeding. The negative results often obtained to not rule out amyloid and most physicians, in view of the pain and hazard involved, are loath to repeat the procedure.

Recently, a new technique has been evolved using the patient's urine sediment examined by electron microscopy. A 250 to 400 ml quantity of clean-catch urine, collected without preservatives, is spun at 10,000 G for one hour and the sediment obtained is fixed in buffered 2 percent glutaraldehyde or buffered 4 percent paraformaldehyde. The

sediment pellet is then processed as for a regular electron microscopy specimen.

In the electron microscope, amyloid fibrils are seen mixed in among the cellular debris and urine crystals. While this exfoliated amyloid does not have the regular pattern seen in an ultrathin tissue section of amyloid, it can be identified readily by its periodicity. Positive findings of exfoliated amyloid fibrils indicate amyloid in the kidneys or urogenital tract. Negative results do not rule out amyloid as in its earlier stages it may not be adjacent to the urinary space. The simplicity of the technique and its noninvasive nature render it ideal in those cases where repeated attempts to establish a diagnosis are advisable on clinical grounds.

The cost of electron microscopy compares favorably with the cost of a biopsy.

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EDITORIALS

A Step in the Right Direction

RECENTLY the chairman of the House of Representatives Ways and Means Subcommittee on Health challenged major health care organizations to develop a voluntary hospital cost containment program. The challenge has been accepted. A national steering committee of "hospital people, doctors, insurers and others with a major stake in hospital cost containment" is being formed under the auspices of the American Medical Association, the American Hospital Association and the Federation of American Hospitals. This is surely a step in the right direction, and one probably long overdue.

For some time it has been a conviction of this writer that complex social problems in our increasingly technologic and interdependent society will never be solved simply by acts of Congress or by imposing regulations more or less based on such acts upon sensitive, everchanging and always interdependent social systems. The health care enterprise in this nation is such a social system and for more than a decade there have been acts of Congress and regulations from the executive branch that have sought to govern it. But this approach has not worked. Health and health care have not improved in proportion to the dollars spent, and in fact the dollars themselves have now become an overriding problem. It seems that legislative and regulatory mechanisms, which tend to seek consistency and more or less standardized solutions to things, are ill-adapted to deal swiftly enough, flexibly enough or sensitively enough to meet everchanging needs which are so different in individual and local situations. But some form of governance is clearly needed. Any sensitive, complex, interdependent system—whether mechanical, physical, biological or human—needs some kind of governance if it is to work smoothly. And it is noteworthy that complicated systems usually have some kind of internal governance, such as an automatic pilot in a large airplane for one example, or the homeostatic mechanisms in the internal environment of biological systems for another. Each of these coordinates a number of forces or sources of power within the system to meet changing situations.

It is a characteristic of this nation that power is divided or shared. In our government there are the executive, legislative and judicial branches, and there are each of these at the federal, state and local levels. This adds up to nine foci of government. But in our complex social systems, of which the health care enterprise is a prime example, there is yet another kind of division or sharing of power. Here there are at least three easily identifiable major sources of power. There is the government with its various branches at the various levels, there are the health system professionals of many kinds, and there are the "consumers" or public. It would seem that the reality of this division of real power in social systems and particularly in the health care system has not yet been fully recognized. Yet there is growing evidence that no one of these groups or bodies is capable of governing the health care enterprise independently of the full participation and cooperation of the others. At present the federal government's effort to regulate every aspect of health care seems fully underway, but it itself is divided—one approach being pitted against another in a fashion which would be ludicrous if it were not so serious—and clearly no one can point with pride at what has been accomplished after more than a decade of all this effort. The health professionals have never really tried to govern the system, perhaps realizing that they never would be able to do so, but at the same time still not realizing that it could never be managed at all without their full participation. And now there is a full-scale attempt to see whether consumers, that is, persons who by definition are supposed not to know anything about the subject, can somehow do better if given an opportunity to exercise consumer power. It seems safe enough to predict that this will not work either, but the power of consumers, that is, the public, is real and certainly an integral part of the complex social system that is the health care enterprise.

One can hope that we are on the verge of a little better understanding of what should be done. In a sense the government has admitted that it is in trouble with its efforts to contain the costs of health care and is calling upon the professionals for help. This is a step in the right direction and it is right that the professional organizations should respond. But if what has been said is true one may foresee that this step will not be enough. It will be necessary to go farther. The power in the health care system is clearly shared among the government, the professionals (defined as those who must run the system) and the consumers or public, whose system after all it is and whom it serves. It is becoming quite safe to say that no one of these groups will ever be able to govern the health care enterprise alone. Ways will have to be found for genuine collaboration among them, which will amount to some kind of internal governance, much as is required for any complex system whether it be physical, mechanical, biological, human or even a combination of most or all of these.

—MSMW

Cholesterol Metabolism and Human Disease

SCOTT GRUNDY'S REVIEW of cholesterol metabolism in man, which appears in this issue, should be useful to all who are interested in the role of cholesterol in atherogenesis and gallstone formation. Cholesterol accumulates locally in both disorders, and full understanding of the mechanisms involved will be required if rational measures for long-term prevention or therapy are to be designed. A necessary first step toward such an understanding would be to trace the pathways by which cholesterol is synthesized, absorbed, transported and excreted. This Dr. Grundy has succinctly done. A second step, particularly in the case of atherogenesis, would be to describe at a molecular level the normal and pathologic effects of cholesterol on cells and tissues. Unfortunately, knowledge concerning these effects is still sparse, although potentially important information has recently been acquired.

Perhaps the most widely appreciated physiologic role of cholesterol is to serve as a precursor of bile steroids and steroid hormones. However, most of the cholesterol in the body does not serve this purpose, but is a component of cell membranes. One role of cholesterol in these membranes is apparently to modulate membrane fluidity and stability.[1] For example, *in vitro* studies of erythrocytes[2] have clearly indicated that selective removal of cholesterol can lead to increased osmotic fragility. A second role of cholesterol in membranes is apparently to influence membrane permeability. Changing the content of cholesterol in artificial vesicles or natural membranes can alter permeability to water soluble solutes.[1] A third role of cholesterol in membranes may be to influence the activity of certain membrane enzymes not necessarily related to cholesterol metabolism. Evidence for this has been obtained both for enzymes of the outer cell membrane[3] and for enzymes of the membranes of cell organelles.[4] In addition, there are indications that membrane cholesterol content can affect such complex cellular processes as endocytosis.[5] How the content of cholesterol itself in membranes is regulated to integrate these various effects is not fully understood, nor is it known which membrane functions would be most seriously disturbed were the mechanisms that regulate cholesterol content to fail.

To understand how dysregulation of cholesterol metabolism in arteries might contribute to atherogenesis poses an even greater challenge. Whereas essential agreement exists concerning some aspects of atherosclerosis, knowledge of its molecular pathology is fragmentary at best. Most investigators would accept a characterization of atherosclerosis[6] that emphasizes the focal accumulation of smooth muscle cells in the arterial intima accompanied by extracellular matrix components, and intracellular and extracellular cholesterol. There also is compelling evidence[7] that coronary heart disease, and presumably deposition of cholesterol in affected arteries, generally reflects the concentration of certain lipoproteins in the plasma. However, from this point on, the picture is obscured by controversy and by lack of detailed information. To account for the accumulation of smooth muscle cells, the following hypotheses have been advanced: (1) atheroma are benign neoplasms where control of smooth muscle cell proliferation has been lost by cell transformation; (2) cells that normally secrete putative inhibitors of smooth muscle cell proliferation diminish as an effect of aging; (3) proliferation of smooth muscle cells occurs in response to a primary injury to the arterial en-

dothelium.[6] None of these hypotheses has so far explained at a molecular level why increased concentrations of low density lipoprotein cholesterol in the plasma should be accompanied by atherosclerosis. Nevertheless, recent data do suggest a potentially fruitful direction for future research. Experiments in nonhuman primates have shown that diet-induced hypercholesterolemia is accompanied by early focal injury to the arterial endothelium.[8] That observation is clearly relevant to the "response to injury" hypothesis concerning atherogenesis because the same diet in the same species later leads to focal accumulations of arterial smooth muscle cells, extracellular matrix components and lipid that closely resemble atherosclerosis.

The possibility that increased concentrations of plasma lipoproteins may injure arterial endothelial cells should be explored further in both clinic and laboratory. Injury to the endothelium is accompanied by decreased platelet survival, which can be measured *in vivo* using existing techniques.[9] In addition, endothelial cells can be grown in tissue culture in the presence of plasma lipoproteins.[10] Therefore, it should be possible eventually to define the unique metabolic characteristics of the arterial endothelial cell and to determine whether critical pathways are adversely affected when the content of cellular cholesterol is experimentally increased. We may then be able to combine the information discussed in Scott Grundy's review with sufficient knowledge of the effects of cholesterol on arterial cells to prove or disprove the notion that cholesterol plays a causal role in atherogenesis.

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Paraquat Poisoning: An Update

In this issue of the Western Journal Robin and co-workers discuss another fatal ingestion of paraquat. This herbicide is marketed as an aerosol, a granule or a water-soluble concentrate. Inhalation of the spray has apparently never been associated with human fatality. The granules contain relatively low concentrations of paraquat and, therefore, are relatively unusual causes for human deaths. The water-soluble concentrates are produced as 20 to 40 percent solutions. Consequently, a small dose of concentrated solution results in a relatively large quantity of ingested paraquat.

Poisoning with concentrated solutions of paraquat is a highly lethal event. Since paraquat was first commercially released, more than 200 deaths have occurred from accidental or suicidal ingestion of the compound.[1] The survival rate following paraquat poisoning has been estimated to be 50 to 65 percent.[2] However, in most survivors clinical evidence of lung involvement never develops. In fact, early reports suggested that once paraquat-associated lung injury could be documented, respiratory insufficiency and, ultimately, death from pulmonary fibrosis were inescapable. More recently, a few reports have emerged that describe survival despite paraquat lung involvement.[3,4] However, the prognosis for patients with paraquat lung is usually bleak.

Considerable research efforts have been devoted to the study of paraquat and its toxic effects. The results of such research along with clinical experience have led to a multidirectional therapeutic approach for victims of paraquat poisoning.[5] Once paraquat has been ingested, immediate and vigorous attempts should be made to (1) minimize absorption of the compound, (2) accelerate excretion of paraquat and (3) modify the tissue effects of absorbed, nonexcreted paraquat.

Minimizing Paraquat Absorption

The principles of gastric lavage are applicable as in other poisonings. More important, following gastric lavage, repeated doses of a specific paraquat adsorbent, fuller's earth, are given concurrently with cathartics every few hours for at least

48 to 72 hours after ingestion. Recently, "gut lavage" (gastrointestinal washout) has been advocated.[6] Using a peristaltic pump, a combination electrolytic solution and specific paraquat adsorbent are transported through the gastrointestinal tract.

Accelerating Paraquat Excretion

Accelerated excretion of absorbed paraquat can be achieved by any of three methods: forced diuresis,[3] hemodialysis[6] or charcoal hemoperfusion.[6] Peritoneal dialysis is ineffective. Recent data have shown that both hemodialysis and hemoperfusion are superior to forced diuresis.[6] When paraquat blood levels are relatively high (36 to 48 hours after ingestion), hemodialysis and hemoperfusion appear to be similarly effective at removing paraquat. When blood levels fall, much greater quantities of paraquat are removed by hemoperfusion.[6] Since the treatment modalities are not mutually exclusive, early attempts to enhance paraquat excretion could and probably should employ a combination of forced diuresis and hemodialysis or hemoperfusion. Subsequently, when blood levels fall, hemoperfusion would appear to be the method of choice. If renal insufficiency and oliguria are present, attempts at diuresis are contraindicated.

Modifying Tissue Effects of Paraquat

Modification of tissue effects is the most difficult and controversial aspect of therapy for paraquat poisoning. In one case report,[7] 1 ml of 20 percent paraquat injected subcutaneously was lethal. Given the fact that minimal quantities of paraquat are capable of causing fatalities, it seems apparent that minimization of absorption and acceleration of excretion could be accomplished relatively efficiently, and yet, death from pulmonary fibrosis could still result from the small amount of paraquat not eliminated by these measures. Although this concept would be most pertinent in patients who ingest large doses of paraquat, attempts to modify and prevent lung injury should be started concurrently with attempts to prevent absorption and hasten excretion of the compound.

Although paraquat is a multisystem poison,[1,5] most fatalities are due to respiratory injury. Hence, measures to modify tissue toxicity are directed toward minimizing pulmonary damage. There are several reasons why paraquat is more toxic to lung than to other tissue:

- Paraquat is actively and specifically accumulated in the lungs against concentration gradients by an energy-dependent process.[1,8] This is important since organ toxicity is related to tissue paraquat concentration.[9]
- Paraquat is tightly bound to nucleic acids and acid mucopolysaccharides.[10] Hence, paraquat is not easily displaced and does not readily diffuse from lung tissue.
- Paraquat undergoes cyclic oxidation-reduction reactions with cellular (or subcellular) constituents and oxygen.[1] The free radical products of these reactions are thought to be toxic to the lung.[1] The high oxygen tension within the lungs facilitates the above mentioned reactions. Furthermore, because one molecule of paraquat can undergo repetitive cyclic oxidations and reductions, large numbers of toxic products may accrue from reactions involving relatively few paraquat molecules.

The most important free radical generated by cyclic oxidation and reduction of paraquat appears to be the superoxide anion (O_2^-).[1] Normally, superoxide anions are rapidly eliminated by an enzyme, superoxide dismutase (SOD), which catalyzes the reaction $2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$.[11] Although H_2O_2 is potentially toxic, available evidence indicates that production of hydrogen peroxide probably does not account for the toxicity of paraquat in animals.[1] On the other hand, the superoxide anion is a highly reactive species capable of causing direct tissue damage.[11] Therefore, one explanation for the pulmonary toxicity of paraquat is that superoxide anions are generated at such a rapid rate in the presence of paraquat and oxygen that cellular SOD is depleted and pulmonary injury occurs.[1]

This theory is the basis for the clinical[5,12] and experimental[13] use of SOD in cases of paraquat poisoning. The clinical data are sparse and difficult to interpret. The experimental data are somewhat better. SOD appears to prolong survival in paraquat-poisoned rats.[13]

The free radical concept is also the basis for therapeutic regulation of inspired oxygen concentration. There is clear evidence in rats that hyperoxic atmospheres accelerate paraquat lung injury[14] and that hypoxic atmospheres ($FiO_2 < 0.21$) retard and prevent lung injury.[15] Accordingly, subatmospheric oxygen concentrations have been administered to human victims of paraquat poisoning.[5,16] Although the data are again sparse,

there are some indications that patients were benefited by this treatment.[5,16]

Despite these advances, many questions still remain to be answered. First of all, the proper dosage and sequence of administration of SOD need to be identified. Secondly, despite the benefits in experimental animals, one objection to the use of hypoxic atmospheres in humans has been the danger of artificially induced arterial hypoxemia. On the other hand, in previous reports of paraquat-poisoned patients, no adverse effects were apparent when arterial oxygen pressure was deliberately maintained in the range of 40 to 60 mm of mercury.[5,16] It is likely that the clinical use of subatmospheric oxygen concentrations requires individualization. In young, previously healthy patients, this type of therapy seems relatively safe.[5,16] In other patients, a different approach may be required. Thus far, the most complicated maneuver has been an unsuccessful attempt to ventilate the lungs with a hypoxic breathing mixture while oxygenating the blood with a membrane oxygenator.[17]

The role of D-propranolol needs clarification. This drug is known to bind to lung tissue.[12] Therefore, by competing for cellular receptors, D-propranolol might (1) retard lung uptake of paraquat and (2) displace already bound paraquat. There is some experimental and clinical evidence to support the role of this drug as antiparaquat therapy.[12,18] Further evaluation seems indicated.

The therapeutic role of corticosteroids (or immunosuppressives) is controversial. I know of no convincing data to support their use. Nevertheless, occasional case reports describe survival following treatment of paraquat poisoning with steroids or immunosuppressives (in addition to other conventional therapy). Controlled experimental data would be welcome.

Finally, several observations suggest that free radical production may be related etiologically to acute paraquat lung but not to the subsequent pulmonary fibrosis.[1] If true, therapy designed to modify free radical generation might conceivably prevent or minimize an early lung injury but not a later fibrotic process. Since most previous experimental protocols studied relatively acute paraquat lung injuries,[13,14] few data are available to evaluate the long-term therapeutic benefits of SOD or hypoxic atmospheres. However, one recent study in rats has shown that continuous hypoxic protection for 7 days is compatible with prolonged survival (longer than 21 days).[15] These experimental data are encouraging.

In conclusion, the paraquat story has evolved rapidly during the past few years. Clearly acceptable techniques have been developed to minimize absorption and hasten excretion of the compound. The present requirement is for further definition and refinement of methods for modifying paraquat's cellular toxicity. The anticipated results would be improved survival for patients ingesting paraquat.

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'Do As I Say'

MOST GOVERNMENTS are elitist and it appears that our federal government is no exception. The evidence is to be found in the fact that a number of burdens which are imposed by law upon the public are not imposed upon federal employees, who work for salaries and wages the same as anyone else, or upon federal institutions which render patient care much the same as many other nonfederal public and private institutions. For

example, federal employees will not be burdened by the very substantial increases about to be enacted in Social Security taxes because Congress has acceded to their desires not to be mandated into the system. No such deference was shown the "elitist" medical profession. And the Veterans Administration hospitals, which in fact provide virtually complete health care services for veterans who choose to use the system, are not required to meet the same utilization standards, quality review and public scrutiny of their finances as is required of other public and private hospitals providing comparable care for federal Medicare and Medicaid beneficiaries.

The conclusion is obvious enough. Our federal government, posing as the servant of the people, is in fact at least to some extent elitist, and adheres to the dictum "Do as I say, not as I do." Is this as it should be? Why should federal employees or federal hospitals providing medical care to civilians be any different from the rest of us? The public is probably less aware of this elitism in our government than it should be.

—MSMW

CASE REPORTS

Refer to: James WS III, Menn SJ, Moser KM: Rapid resolution of a pulmonary embolus in man. West J Med 128:60-64, Jan 1978

Rapid Resolution of a Pulmonary Embolus in Man

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BASIC TO diagnosis and management in cases of suspected or documented pulmonary emboli is an understanding of the natural history of this disease and its response to treatment. One critical aspect of natural history is definition of the speed with which emboli can resolve. A number of reports have appeared quantitating the rate of resolution of pulmonary emboli during anticoagulant therapy in dogs[1-4] and in man.[5-13] In dogs emboli appear to resolve faster than in humans; the most rapid resolution of a documented embolus reported in man is seven days.[6] We wish to report the case of a patient with massive pulmonary emboli in which one large embolus resolved within 51 hours of the start of heparin therapy.

Report of a Case

A 59-year-old man was admitted to the Veterans Administration Hospital in San Diego on August 19, 1975, because of left-sided weakness for three hours.

He had been in good health until 1971 when he noted the acute onset of left-sided weakness, which resolved partially over the following year. Two weeks before the present admission there was sudden onset of weakness in his left hand and foot, which resolved completely in 30 minutes. On the evening of admission there occurred acute onset of weakness in his left foot and numbness of his left hand, without other symptoms.

He had smoked one pack of cigarettes a day for 20 years but had stopped in 1945. He said that there had been no respiratory symptoms.

On admission he appeared in no distress; temperature taken orally was 36.9°C (98.5°F); heart rate, 100 beats per minute; blood pressure 160/80 mm of mercury, and respirations, 20 per minute. There were no carotid bruits. The chest, heart and abdomen appeared normal. There was no evidence of venous disease in the legs. The left hand and ankle were weak; the remainder of the neurologic examination gave findings within normal limits.

Pertinent negative laboratory data included complete blood count, liver function tests, blood urea nitrogen, blood glucose, electrolytes, prothrombin and partial thromboplastin times, and roentgenogram of the chest.

A diagnosis of an incomplete right middle cerebral artery occlusion was made, and the patient was admitted to the neurology service, where heparin therapy was begun. Attempts at lumbar puncture were unsuccessful. After two days, heparin therapy was discontinued in anticipation of cerebral angiography; however, the patient then noted the development of headaches followed by left hemiparesis, and cerebral angiography was cancelled.

Over the ensuing 19 days the patient was confined to bed and there was little resolution of neurologic deficits. His course was complicated by intermittent spiking fevers of unknown cause, hyperglycemia and hyperosomolarity. He was treated with steroids, glycerol, penicillin, insulin and bronchodilators by intermittent positive pressure. On September 11 he became hypotensive, and subsequently was moved to the medical intensive care unit. On transfer, his temperature was 39.4°C (103°F); blood pressure, 100/60 mm of mercury; heart rate, 120 beats per minute; respirations, 28 per minute. Tubular breath

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Partially supported by UCSD Pulmonary SCOR Grant No. HL14169.

Submitted, revised, May 25, 1977

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sounds were noted in the right middle and lower lung fields, but no rales. A left hemiparesis persisted. Lumbar puncture disclosed xanthochromic fluid with a normal leukocyte count. Arterial oxygen pressure (Po_2) with the patient breathing 100 percent oxygen was 268 mm of mercury; carbon dioxide pressure (Pco_2) was 34 mm of mercury, and pH 7.36. A roentgenogram of the chest was interpreted as showing "minimal haziness" in the right upper lobe. A Gram stain of a transtracheal aspirate showed many polymorphonuclear leukocytes and Gram-negative bacilli. The patient was thought to have either a Gram-negative pneumonia or thromboembolism.

Figure 1.—Technetium 99m perfusion lung scan done September 11, 1975; anterior views. Perfusion defects at the right apex and at the right and left bases are shown.

A technetium 99m perfusion lung scan on September 11, 1975, showed large perfusion defects in both posterior basal regions and in the right upper lung field (Figure 1). Ventilation scanning could not be done because of the patient's critical condition. Because he was considered to be at high risk for resumption of anticoagulant therapy because of probable recent intracerebral bleeding, a pulmonary arteriogram was carried out that evening (ten hours after the onset of hypotension) to clarify the diagnosis (Figure 2). It showed a large embolus in the right pulmonary artery at its bifurcation into upper and lower divisions, with extension into multiple vessels in the right upper lobe; selective injection of the left pulmonary artery showed a large thrombus in the lower divisions with complete cutoff of vessels to the lower lobe. Despite the extensive bilateral emboli, runoff of contrast material from each pulmonary artery was good.

Intravenous administration of heparin was begun (an initial bolus of 10,000 units followed by

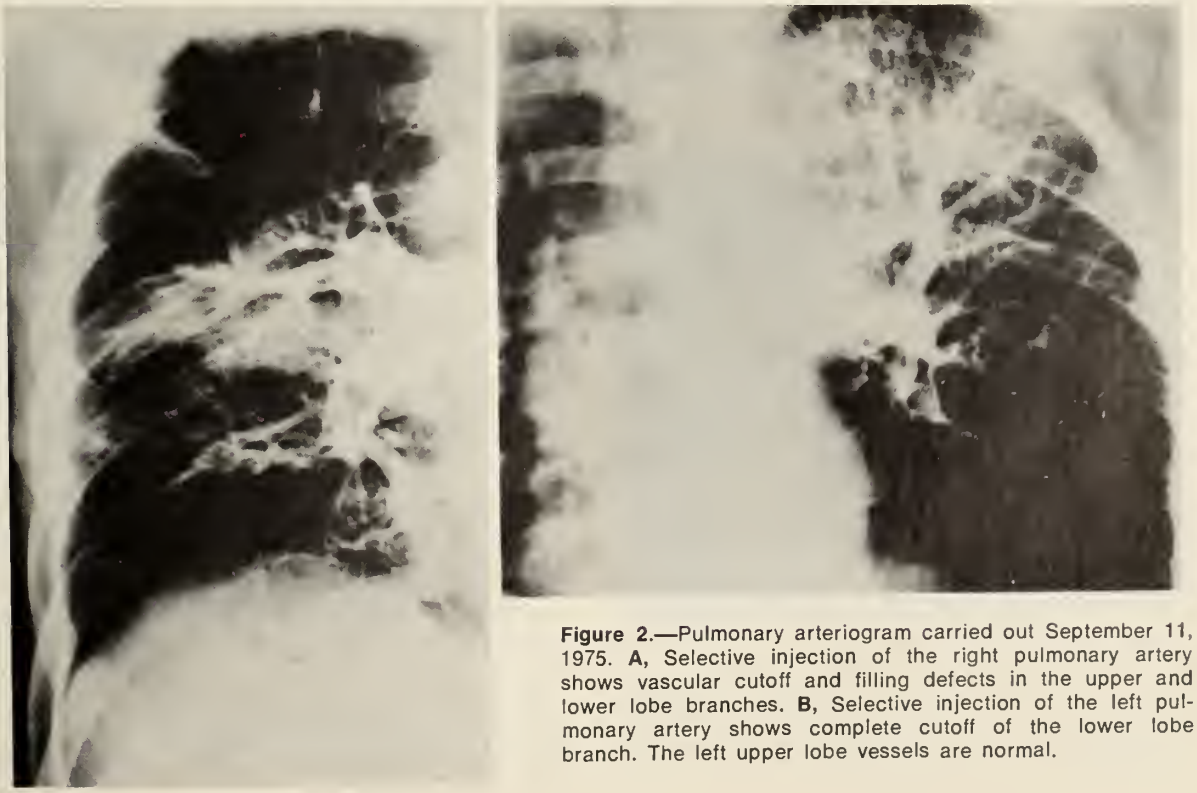

Figure 2.—Pulmonary arteriogram carried out September 11, 1975. **A,** Selective injection of the right pulmonary artery shows vascular cutoff and filling defects in the upper and lower lobe branches. **B,** Selective injection of the left pulmonary artery shows complete cutoff of the lower lobe branch. The left upper lobe vessels are normal.

constant infusion of 1,000 units per hour). A Swan-Ganz catheter with thermodilution sensor was inserted into a right lower lobe arterial branch; the pulmonary artery pressure was 25/7 mm of mercury (mean, 16 mm of mercury). Multiple attempts to measure wedge pressure were unsuccessful. Cardiac output (thermodilution) was 4.1 liters per minute. With 40 percent oxygen given by mask, arterial Po_2 was 126 mm of mercury, Pco_2 was 35 mm of mercury and pH was 7.36.

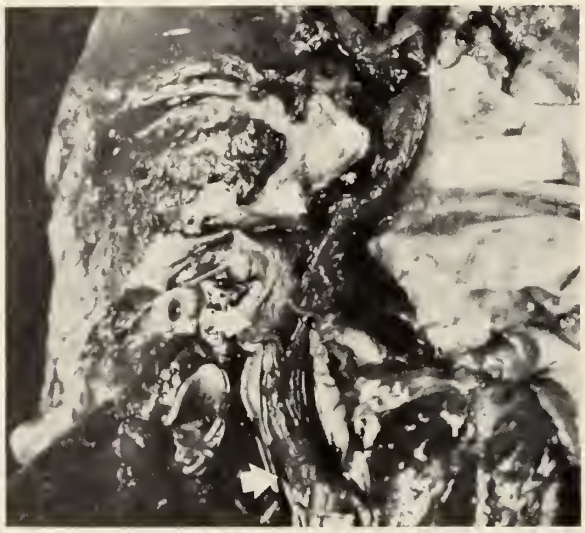

Figure 3.—Appearance at autopsy of the right pulmonary artery thrombus. The pulmonary arterial system has been opened and the right lung and pulmonary artery are viewed from the medial aspect. A large thrombus **(arrows)** is seen filling the right upper and lower lobar branches.

Figure 4.—Appearance at autopsy of the main pulmonary trunk and its branches. The right side is pictured as seen in Figure 3; the left lung and pulmonary artery are viewed from the medial aspect and are seen to be free of thrombi. The trachea lies in the middle of the figure.

Over the next 36 hours, increasingly higher inspired oxygen fractions were required to maintain an adequate arterial Po_2. A roentgenogram of the chest showed persistence of the right upper lobe haziness and a new infiltrate in the right lower lobe. Progressive hypoxia and respiratory acidosis developed, with the arterial Pco_2 rising to 55 mm of mercury; elective nasotracheal intubation was carried out, apparently without incident. However, the patient became hypotensive soon after intubation and an idioventricular rhythm developed. Physical findings suggested a left pneumothorax, and a chest tube was inserted.

Attempts to maintain an adequate cardiac output were unsuccessful and the patient died at 5 PM, 51 hours after hypotension was first diagnosed.

At autopsy, attended by the physicians who had managed the patient, the large embolus shown by angiography in the right pulmonary artery was found intact (Figure 3). The macroscopic organization of the clot and its firm adherence to the vascular walls indicated it to be clearly antemortem in origin. The left main pulmonary artery, however, was free of thrombi (Figure 4). Furthermore, extensive dissection of the left pulmonary arterial tree disclosed no macroscopic evidence of antemortem thromboemboli. Hemorrhagic infarctions of both lower lobes, extending to pleural surfaces, were present; a large mural thrombus was found in the right atrium, but no underlying evidence of infarction or injury to the atrial tissue was evident. No breaks in the tracheal, bronchial or pleural surface which might explain the acute left pneumothorax were found.

Discussion

The speed with which pulmonary emboli can resolve has both therapeutic and diagnostic implications. With respect to therapy, speed of resolution is one determinant of the duration of therapy. The twin purposes of anticoagulant therapy in venous thromboembolism are to halt the growth of thromboemboli and reduce the likelihood of recurrence. Resolution of pulmonary emboli indicates that the first objective has been achieved; resolution of venous thrombi helps to achieve the latter.

Diagnostically, embolic resolution rate bears upon two important and frequently-raised questions: (1) how rapidly can an abnormal perfusion

scan secondary to embolism return to normal and (2) how quickly must a pulmonary angiogram be done so that a "false negative" result due to embolic resolution can be avoided?

The case reported here illustrates the fact that resolution, even of major emboli, can occur rather swiftly in man. The documented emboli had resolved completely within 41 hours after the angiogram.

In dogs we have shown that complete resolution of massive fresh emboli can commonly occur within a day, and that the resolution rate is accelerated by administering heparin (presumably because heparin halts thrombus growth and allows the fibrinolytic system to function unopposed).[4]

Data in humans are difficult both to obtain and to quantify precisely. The age of the thrombus before detachment is unknown and aged emboli are known to resolve more slowly than recently-formed emboli.[13,14] Further, the exact time at which the embolus occurred is difficult to pinpoint; therefore, the period between embolism and resolution contains a presumptive element. And, finally, the required sequential observations can be made in man only during rigorously controlled investigational protocols or under unusual clinical circumstances, as in our patient.

The word *resolution* has been used here and in other reports to describe the reduction (or total disappearance) of embolic obstruction, permitting reestablishment of pulmonary blood flow. Resolution does not imply the mechanisms responsible because, in man, it is virtually impossible to distinguish among them if the patient survives. Three mechanisms can lead to resolution: fibrinolysis (dissolution), fragmentation with distal migration of the fragments, and organization. In our patient, autopsy findings documented that resolution of the emboli on the left did not occur by organization; furthermore, no emboli were recovered from the smaller distal vessels by further dissection of the left lower lobe. Consequently, our presumption is that fibrinolysis did occur. But, whatever the mechanism, the central diagnostic fact remains that a large embolus shown to be present by angiogram on one occasion would not have been seen had an angiogram been repeated 41 hours later.

How can it be that one embolus (on the left) resolved while others (on the right) did not? Multiple factors may condition the rate of thrombus resolution, particularly by fibrinolysis.[4] Perhaps the most important factor is the age of the thrombus. It has been shown both experimentally and clinically that older thromboemboli are substantially more resistant to spontaneous or urokinase-induced lysis than are fresh thromboemboli.[13,14] Since the emboli on the right in this patient had undergone some organization, we believe we can construct a rational sequence to explain what occurred in this patient. At some time during the period before the episode of hypotension on September 11, the patient likely had one or more episodes of unrecognized embolization to the right lung which did not resolve. On September 11 an embolic recurrence occurred and the embolus had no alternative but to enter the vessels of the left lung. Our assumption is that this event led to his hypotensive episode. Subsequently, this "fresh" embolus underwent dissolution, perhaps enhanced by institution of heparin therapy.[4] Assumption of such a sequence seems justified in this patient, particularly since we have previously documented that different rates of embolic resolution do occur in man.[16]

Previous reports of resolution of pulmonary emboli in man have used repetitive perfusion lung scanning,[9,10] pulmonary angiography,[5-7] or both,[8,11,13] to document and quantify degrees of resolution. Poe and co-workers reported the earliest resolution of blood flow through an occluded lobar artery in man in four days, based on scan.[9] Almost all of their patients were receiving heparin, and, as was done here and in the Urokinase Pulmonary Embolism study, the recovery of perfusion was timed from the onset of symptoms, presumably coinciding with the occurrence of the embolic event. Complete resolution of angiographic evidence of thromboembolism has occurred after 7 days of heparin therapy in a patient in one report[6] and 14 days in a patient in another.[12]

The perfusion scan and the pulmonary angiogram do not, of course, provide the same data regarding resolution rates. The scan documents return of blood flow, not restoration of total luminal patency. Normal distal blood flow occurs when 20 percent or more of the pulmonary artery lumen has been restored.[15] Therefore, the findings on scan can return to normal when an angiogram still shows a significant luminal filling defect, as we have shown.[16]

The present case, based on angiographic and autopsy observations, does not suffer from such

interpretive limitations. Clearly, emboli can resolve in man within the time period reported here. How often resolution occurs at this rate—or within a shorter span of time—remains to be defined. Each such case will further expand our ability to define the time-based rate of embolic resolution more clearly.

Summary

A 59-year-old man admitted to hospital with intracerebral bleeding was shown to have massive pulmonary thromboemboli in the right upper, right lower and left lower pulmonary arterial lobar branches by perfusion lung scanning and by pulmonary angiography. Anticoagulation with heparin was begun but death occurred two days later. At autopsy, the right-sided emboli were intact but no evidence of emboli in the left pulmonary arterial circulation was present. Since death occurred 51 hours after onset of symptoms suggesting pulmonary thromboembolism, this represents the most rapid resolution of a pulmonary embolus reported in man.

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Refer to: Haburchak DR, Davidson H: Anorectal lesions and syphilitic hepatitis. West J Med 128:64-67, Jan 1978

Anorectal Lesions and Syphilitic Hepatitis

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
FTA-ABS = fluorescent treponemal antibody absorption test
RPR = rapid plasma reagin (test)

CLINICALLY APPARENT HEPATITIS is an uncommon manifestation of secondary syphilis. When hepatic dysfunction is the major feature of syphilis, it may be difficult to recognize the cause, particularly when primary lesions are covert or occur in unfamiliar locations. The following case illustrates such an occurrence.

Report of a Case

A 33-year-old previously healthy man noted the development of painful defecation without change in stool character while he was in Korea in November 1975. Approximately two weeks later he was admitted to an Army hospital in Korea where sigmoidoscopy done under general anaesthesia showed the presence of a "small lesion" at the anal verge, a 1 cm "lesion" in the distal rectum and a 2 cm "mass" at 8 cm. Digital examination disclosed enlarged lymph nodes at the pelvic inlet. A rapid plasma reagin test (RPR) done on December 2 was positive, but a repeat RPR and a fluorescent treponemal antibody absorption test (FTA-ABS) on December 9 were

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Submitted, revised, April 25, 1977.

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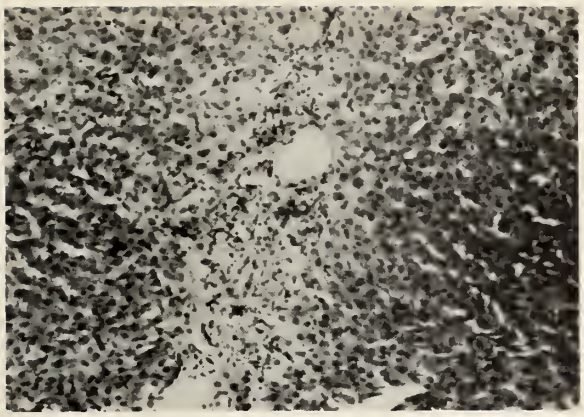

Figure 1.—Photomicrograph of liver tissue from patient with secondary syphilis showing periportal inflammation with polymorphonuclear leukocytes. (Hematoxylin and eosin stain, reduced from ×100).

negative. A biopsy study of a rectal lesion showed only chronic inflammatory infiltrate and plasma cells in the lamina propria. Findings on a barium enema were normal. The patient was discharged on December 12 with no specific diagnosis or treatment.

On January 6, 1976, he was readmitted with fatigue, sweats, pruritus and weight loss. Rectal pain had continued, and minimal rectal bleeding had developed. Findings on physical examination were unchanged and a repeat proctoscopic examination showed the presence of a mass at 6 cm. Biopsy results were again nonspecific. Laboratory data showed a leukocyte count of 7,100 per cu mm, hematocrit of 45 percent and a sedimentation rate of 27 mm per hour. Analysis of urine showed 4+ protein and 3+ bile. RPR's on January 6 and January 14 were negative. All the following studies were negative: rheumatoid factor, antinuclear antibody, MONOSPOT® (Ortho, Raritan, NJ), hepatitis B surface antigen, Bence-Jones urinary protein, serum protein electrophoresis and stool examinations for ova and parasites. Liver profiles are shown in Table 1. No abnormalities were shown on an x-ray study of the chest and on an upper gastrointestinal series. A lymphangiogram showed enlarged iliac and paraaortic lymph nodes with some scalloping felt to be indicative of inflammation or infiltration. The patient was transferred to Letterman Army Medical Center on February 12, 1976, with a presumptive diagnosis of lymphoma and hepatitis.

Additional history disclosed contact with a female prostitute in Korea and digital manipulation of the rectum by the prostitute during intercourse. The patient stated there had been no homosexual contact, foreign body manipulation of the rectum, drug abuse or excessive ethanol intake. He received no drugs during his hospital stay in Korea except diphenhydramine hydrochloride occasionally for pruritus.

On physical examination the patient appeared chronically ill. Temperature was 38°C (100.4°F). Scleral icterus and a mucus patch over the left tonsil were present. Liver span was 15 cm and it was slightly tender to percussion. The spleen tip was palpable. Multiple small cervical and inguinal lymph nodes were present. The skin showed a papulosquamous eruption of the palms and soles. Rectal examination showed pronounced tenderness and on proctoscopy a small 2 mm ulcer was noted in the anterior rectal wall at 2 cm.

Laboratory investigation showed a hematocrit of 43 percent, leukocyte count of 7,400 per cu mm and a reticulocyte count of 1.6 percent. Analysis of urine showed no protein. A Venereal Disease Research Laboratories' test (VDRL) titer was 1:64 and an FTA-ABS was positive. Cerebrospinal fluid (CSF) examination showed a protein content of 52 mg per 100 ml, glucose value of 64 mg per 100 ml, 2 polymorphonuclear leukocytes and 26 lymphocytes per cu mm. Cultures of CSF for bacteria, acid-fast bacilli and fungi were negative. The CSF-VDRL was negative. The following studies were negative or normal: prothrombin time, partial thromboplastin time, serum haptoglobin, Coombs test, antimitochrondrial antibody, serum copper, hepatitis B surface antigen, alpha fetoprotein, x-ray film of the chest and liver-spleen scan. Serum protein electrophoresis showed polyclonal gammopathy. Intermediate strength tuberculin, candida and streptokinase-streptodornase skin tests were negative. Dark-field examinations of mucus patches and rectal lesions were not carried out.

A percutaneous liver biopsy specimen exhibited a small degree of diffuse Kupffer cell hyperplasia and an infiltration of polymorphonuclear leukocytes in the portal triads (see Figure 1). The liver parenchymal cells appeared normal and silver stains for treponemes were negative. An attempt was made to stain for treponemal antigen using an indirect fluorescein labeling technique; however, this was unsuccessful possibly due to availability only of formalin fixed liver tissue.

Because of CSF pleocytosis, the patient was treated with intramuscular benzathine penicillin,

2.4 million units per week for four weeks (see Table 1). Six hours after the first injection, a shaking chill and a temperature of 38.8°C (101.8°F) developed, but there was no evidence of hypotension. The skin lesions cleared within one week, but serum glutamic oxaloacetic transaminase (SGOT) and alkaline phosphatase values remained elevated when studies were done one month after therapy. Spinal fluid and rectal examinations on March 16 showed no abnormalities.

The patient was discharged and transferred to another facility for outpatient follow-up. When seen in December 1976, the patient was in good health and, with the exception of minimal hyperbilirubinemia, a liver profile is normal. VDRL remains positive at a titer of 1:2.

Discussion

Reports of hepatitis associated with early syphilis have suffered from an inability to completely exclude other causes of hepatitis.[1] This patient is thought to have had syphilitic hepatitis based on the following indications: lesions in the rectum consistent with primary syphilis, clinical findings of secondary syphilis, positive serologic studies, a battery of studies to exclude other causes of hepatitis, negative history for drug-induced hepatitis, biopsy findings not characteristic of viral hepatitis and a response to penicillin therapy. The patient may also have had early syphilitic nephrosis with reported 4+ urine protein and possible neurosyphilis with negative CSF-VDRL.

Primary lesions of syphilis in the rectum usually occur by way of anal intercourse and are most commonly seen in male homosexuals.[2] Although this patient's statement that homosexual contact had not occurred might be viewed with skepticism, his history suggests that digital manipulation may be another means of transmitting the disease. This case does emphasize the importance of a sexual history in the evaluation of rectal lesions.

Lesions in this case were described as multiple, small, painful masses in the distal rectum. Ulcers or heaped-up painful masses have been described as characteristic of anal syphilis by Gluckman.[2] Failure to carry out dark-field examination of the rectal lesion coupled with variable serologic results caused an initial impression of lymphoma of the rectum, a rare diagnosis, seemingly confirmed by lymphangiography. It is well known that both treponemal and nontreponemal tests may be negative in primary syphilis, therefore a dark-field examination of all rectal lesions of obscure cause is important as well as serologic evaluation.

In previously described cases of early syphilis associated with hepatitis, anorectal lesions have been common. Specifically an anorectal lesion has been found in six,[3-8] a penile primary in one[9] and no primary found in three.[10-12] Unfortunately in Feher's large series of 17 patients with syphilitic hepatitis, the sites of primary lesions were not specified.[13] This preponderance of anorectal lesions suggests that the mode of acquisition of syphilis may be important in the development of clinical hepatitis. Perhaps this represents a delay in recognition of primary disease by the patient or physician, resulting in lack of early therapy. An attractive but speculative hypothesis is that rectal involvement may lead to an early and substantial treponemal invasion of the liver via the portal venous system.

The clinical manifestations of syphilitic hepatitis are nonspecific—fever, malaise, weight loss and tender hepatomegaly. An unusual elevation of alkaline phosphatase compared with a modest elevation of transaminase occurred in our patient and has been noted by others.[7-12] The degree of

TABLE 1.—*Liver Enzyme and Function Tests in a Patient With Secondary Syphilis and Hepatitis*

	Jan				*Feb*				*Mar*					*Dec*
	6	12	20	28	12	19	21*	27*	2	5*	8	12*	17	10
Total bilirubin (mg per 100 ml)	2.7	2.3	5.5	8.5	16.4	11.0	..	6.4	4.5	..	3.6	..	2.0	2.0
SGOT (IU) (normal <40)	120	186	175	150	151	166	..	134	107	..	..	..	186	31
Alkaline phosphatase (IU) (normal <92)	230	399	390	275	580	740	..	580	620	..	600	..	348	64
Albumin (grams per 100 ml)	..	..	..	..	2.7	2.8	..	2.4	2.8	..	2.9	..	4.1	5.1

SGOT = Serum glutamic oxaloacetic transaminase

*Benzathine penicillin dose, 2.4 million units given intramuscularly

hyperbilirubinemia in this patient is noteworthy with only modest elevations noted by most authors.[4-9,13]

Microscopic examination of the liver in this case showed periportal inflammation with polymorphonuclear leukocytes and Kupffer cell hyperplasia. Previous reports have described nonspecific focal inflammation in periportal and central venous regions,[4,7,10,12,13] Kupffer cell proliferation,[4,10,13] granulomatous hepatitis,[6] cholestatic hepatitis[4,5,7] and small areas of focal liver cell necrosis.[7,13] Spirochetes have been shown to be present in the liver specimens of nine patients, seven of these from Feher's series.[13] Findings on Warthin-Starry silver stain for spirochetes and indirect treponemal fluorescent antigen staining were not helpful in the current case. The latter may have been unsuccessful because formalin fixed tissue was utilized. Further investigation of syphilitic hepatitis should include fluorescent staining for treponemal antigen on non-formalin-fixed tissue. This could add specificity to the diagnosis and obviate obtaining a wide spectrum of tests to exclude other causes of hepatitis. Serology for viral hepatitis should be done, however, to rule out concomitant disease.

The natural history of untreated early luetic hepatitis is not known. Hepatic gummata are well described, but are now rarely seen and their relationship to early syphilis is not clear. Chronic active hepatitis,[13] hepatoma[14] and Budd-Chiari syndrome[15] have been postulated to result from syphilis, but the evidence is weak.

At present there is no standard antibiotic regimen for hepatitis associated with early syphilis. Cure has resulted from administration of 2.4 million units of benzathine penicillin in one patient,[4] but in most cases larger doses of penicillin have been used.[3,5,6,8,9,11] Although the CSF-VDRL determination in this case was nonreactive, the patient was treated with a dosage of penicillin currently deemed adequate for neurosyphilis because of the CSF pleocytosis.

After institution of therapy with penicillin, a Jarisch-Herxheimer reaction can be expected, as occurred in this case.[4] Laboratory evidence of hepatitis generally resolves over a few weeks.[4,6-9]

Summary

In a patient with undiagnosed painful rectal lesions signs of hepatitis and secondary syphilis occurred later which responded to therapy with penicillin. A battery of liver tests disclosed disproportionate elevations of alkaline phosphatase and total bilirubin. A liver biopsy study showed periportal inflammation with polymorphonuclear leukocytes and Kupffer cell hyperplasia. The preponderance of primary anorectal lesions in syphilitic hepatitis suggests that lack of recognition of these lesions (with a resultant delay in therapy) and the anatomic location are important in its pathogenesis. A detailed sexual history, dark-field examination and serologic studies should be done in all patients with rectal lesions of uncertain cause.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Traumatic Fibromyositis

To the Editor: An article entitled "Traumatic Fibromyositis, A Critical Review of an Enigmatic Concept" by Laurence M. Weinberger, MD, appeared in the August 1977 issue of the Western Journal. As my work has been mentioned repeatedly in this article I would like to make several comments.

Dr. Weinberger rather than attempting to understand the problem of fibromyositis by appropriate investigative techniques, has elected to deny it completely—which has been the attitude of some other physicians throughout the past century. In his article he has made no mention of our histological findings. These as well as the records of the LDH isoenzyme changes, which he denies, are available for review and it does not make sense to ignore these findings.

While Slocumb[1] described fibrositis as the most common form of acute and chronic rheumatism, and stated that primary fibrositis accounted for 11 percent of the consultations for rheumatic symptoms at the Mayo Clinic, we find Dr. Weinberger stating that "in many instances the signs and symptoms were probably confused with the phenomena of rheumatoid arthritis." This is a good example of the attitude of the author that all authors of previous interest in this condition were confused.

Our statement of trauma being the requirement is clearly stated in my paper as a hypothesis (or an assumption made for the sake of discussion). To attack a hypothesis should be done by presenting a different hypothesis not by mere denial of the problem.

Finally, the continued denial of this problem by Dr. Weinberger and others, while physicians' offices and hospitals are crowded with patients suffering from myofibrositis, will not benefit anyone. On the other hand, sincere efforts of some of us to clarify the cause of this condition may eventually lead to its control by prevention and appropriate therapy.

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REFERENCE

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* * *

Dr. Weinberger Responds:

To the Editor: As I now understand it, Dr. Awad views trauma only as a working hypothesis in order to explain the features and pathogenesis of his newly minted disease, interstitial myofibrositis. In his paper,[1] however, the hypothesis is expressed as a vigorous conclusion: "The hypothesis (of interstitial myo-fibrositis) has one requirement, trauma."[1(p452)] Again, "a hypothesis proposing that myo-fibrositis results from trauma is presented."[1(p453)]

If one accepts Dr. Awad's apparently straightforward assumption that trauma is the root cause of interstitial myo-fibrositis, then one is confronted by unexpected consequences and biological perplexities. These are:

- That trauma—according to Awad—sooner or later, causes the appearance of masses of amorphously staining mucoid substance (tentatively identified as muco-polysaccharides) between otherwise normal muscle fibers and fascicles.
- This histiological observation is thought to be responsible for increased consistencies within the muscles of afflicted patients that can be detected only by sophisticated palps probing through oiled skin.
- The process linking the clinical and histologic findings with the original trauma is described by the following sequence of hypothecated events: (p 449, summary, lines 14-21) "Trauma leads to extravasation of platelets which releases serotonin leading to vasoconstriction and localized edema

in the muscles. Edema *may* result in degranulation of the mast cells and the release of histamine and heparin. Histamine *attempts* to *counteract* vasconstriction and heparin *may* prevent clotting of the extravasated blood and lymph. Several aspects of the treatment of myo-fibrositis support this theory" (Italics mine and indicate links filled by speculative connectives).

All these events are described as occurring without the phenomena of inflammation, without alteration of muscle fibers or fibrils, without vascular reactions, without reparative processes and without abnormal electrical activity. Yet, Dr. Awad uses the suffix "itis" and the locational identification, "interstitial." Such a theory, complex beyond the usual limits of biology or the experience of reality, succeeds only in proving (sic) the original assumption—for example, trauma is the cause of myo-fibrositis. This is a clear example of circular reasoning abetted by sleight-of-hand usage of words.

Dr. Awad's group further offers attempts to give a biochemical interpretation of the pathogenesis conceived above by assuming "Therefore myo-fibrositis could be considered as an inflammation of the interstitial connective tissue of the muscle rather than as primarily a muscle disease."[2(p22)] The argument is pursued by "the assumption is supported by our present findings that in nearly all examined patients, the serum enzymes did not show a significant rise."[2(p27)] Only LDH iso-enzymes showed peculiarities of distribution not reflected in total values.

This, in my view, defies explanation. One also includes the final comment "In patients treated with massage and aspirin, the LDH enzymes were reversible indicating the specificity of these changes to myo-fibrositis."[2(p27)] Everything now seems to come together with the implication that this novel disease yields to heat, massage, aspirin and ultrasound, which happen to be exactly the elements supplied by physical therapists.[1(p452)]

In conclusion, I will hold fast to my view, as outlined in my article in the August issue, that traumatic myo-fibrositis (and cogeners) is a myth created by those who invent diseases by naming and treating them.

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Traumatic Fibromyositis or Myofascial Trigger Points?

To the Editor: In his enthusiasm to debunk the name "Traumatic Fibrositis" in his article in the August 1977 issue, Dr. Weinberger appears to me to throw the baby out with the bath water. The term *fibrositis,* traumatic or otherwise, has a long history of confused definitions.[1] It is considerably more deserving of his criticism than are the concepts identified with the term *myofascial trigger points*[2] which he apparently does not understand. The plethora of terms that cover a spectrum of definitions and concepts scarcely justifies exclusively blaming the patients' psyche for their pain of obscure origin when the facts clearly indicate otherwise. What are the facts?

I agree that the identification of a myofascial syndrome, and evaluation of its response to treatment depend largely on the patient. Is it wrong to listen to what the patient has to tell us? However, the final localization of a trigger point depends on the physical examination. Not all phenomena associated with myofascial trigger points are subjective. Diagnostically, the electromyographic activity of the *jump response* to snapping palpation of the trigger point in a palpable band is completely objective. The jump response is commonly visible or palpable when the examiner looks for it. Similarly, the jump response during needling of the trigger point and the subsequent softening of the palpable band with loss of jump response immediately afterward are purely objective. Increased range of motion and recovered functional activity following successful treatment are additional semiobjective responses.

I agree that the specific afferent and efferent feedback mechanisms that would perpetuate myofascial trigger points have not yet been established. Muscle spindle or C fiber afferents and autonomic efferents are likely candidates, but critical experiments to confirm or refute these have yet to be reported, to my knowledge. Frequent immediate relief or recovery in response to one of the following procedures speaks to such a mechanism: (1) mechanical disruption of the trigger point by needling with or without a local anesthetic, (2) spread of local anesthetic to the trigger point without evidence of needle penetration of the trigger point, (3) sustained progressive firm pressure on the trigger point, (4) during stretch, proper application of vapocoolant spray to the skin that overlies the muscle fibers, thereby in-

hibiting the painful spasm that would otherwise be induced by attempted stretch to full range of motion.

True, critical experiments to show how trauma initiates the neuromuscular hyperirritability of a trigger point have not been reported to my knowledge. However, the patients themselves implicate a traumatic cause when they so commonly can pinpoint the onset of their pain problems to a specific event, often months or years before. They frequently can describe, when asked, a precisely-remembered movement or mishap that would have overloaded the muscle(s) containing the trigger points(s).

To assume that referred pain must follow accepted boundaries of nerve distribution puts one on the horns of a false dilemma. Kerr[3] showed there to be sensory spinal pathways that are structured for both intersegmental transmission and disinhibition that could logically cause referred pain by convergence projection and convergence facilitation. Similarly, there is no basis to assume that the initial phase must be pathological. Indeed, the concept of an initial stage of neuromuscular dysfunction which may subsequently develop structural pathology is firmly rooted in English,[4,5] German[6,7] and Russian[8] literature which transcends simple "wordsmithing."

The implication that only a few muscles of the body show the cardinal features of myofascial trigger points[2] is misleading. Most, if not all, of the accessible muscles in all parts of the body may become involved, some more commonly than others. Each muscle has a specific locus, or loci, which characteristically develop trigger points. Injection of hypertonic saline into a normal muscle evokes referred pain that has essentially the same pattern characteristic of trigger points that develop in the same portion of the same muscle.[9-11]

The author's statement that there are no observable pathological alterations ignored the meticulous, comprehensive study by Miehlke and co-workers[12] using frozen sections from 77 patients which confirmed and extended the findings of a previous well-documented study in 24 biopsies.[13] Both studies reported myopathic changes. The later study showed progression of pathology with increasing severity of symptoms. Dr. Weinberger's statement also ignored the recent ultramicroscopic studies by Awad[14] and by Fassbender and Wegner;[15] the latter is now available in English.[16] Negative biopsy findings quoted by the author resulted from studies of tissues other than muscle, or studies that failed adequately to identify sampling criteria and the stain used, or studies in which random samples of muscles or tissue unrelated to muscle were taken. One should not expect to find specific myofascial trigger point pathology in nonmuscular tissue, or in parts of the muscle not associated with trigger points. One must take seriously the more than 100 consistently myopathic biopsy results compared with only 8 or so adequately described negative results,[1] particularly when the difficulty in accurately locating the site in order to do a biopsy study of a trigger point is considered.

A summary of the world literature by Popelianskii and associates[8] includes an extensive Russian literature rarely, if ever, referred to in English. Based on extensive clinical experience, radioisotope studies of local circulation and chronic lesions induced in rats, they concluded that the ubiquitous nonarticular disease of soft tissues starts as a functional neurodystrophic or algic stage. It progresses to an organic or musculodystrophic stage as shown by Mielke and co-workers.[12] They showed that one should not expect to observe pathological changes in biopsy specimens of muscles that are still in the initial dysfunction stage unless the special technique of frozen sections and a stain specific for fat is used. The second paper[17] presents electromyographic records of the jump *response*. That paper erroneously used the term "jump sign" which already had been introduced by Kraft and associates[18] to describe a much different phenomenon. The presence of the jump response substantiates the neuromuscular hyperirritability of trigger points. Frequently, it is necessary to examine trigger points by a specific technique of snapping palpation to elicit the physical sign of the jump response. Otherwise, the palpable band and the trigger point it contains may easily be overlooked.

The bath water is still cloudy, but the baby is worth saving.

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Survival in Lung Cancer

To the Editor: The report from Travis Air Force base (Reynolds RD, Greenberg BR, Hill R, and associates: Survival in lung cancer. West J Med 127:190-194, Sep 1977) describing survival in patients with bronchogenic carcinomas following primary diagnosis at their institution was of some interest. Lacking, however, are any specifics about the treatment given to their patient population. Nonetheless, a rather misleading general statement "Radiotherapy did not prolong survival" appears as the last sentence in their lead abstract.

Later, we learned that they actually studied only the effect of postoperative irradiation on a relatively small group of patients with stage II and III disease. It should be noted that their negative conclusions contradict the findings of Kirsch[1] and Green and co-workers[2] from two separate studies involving patients with positive regional nodes. Pattersons's often quoted study[3] showing no benefit from postoperative irradiation did not separately analyze the effect on patients with involved nodes.

The therapeutic decision most often challenging the oncologist and the referring physician involves the efficacy of radiation therapy in the better risk, asymptomatic patient, with inoperative or unresectable local-regional disease. The published results of Smart and Hilton,[4] Guttman,[5] and Aristizabal and Caldwell[6] all describe clearly beneficial effects of primary irradiation on survival in this type of selected patient with lung cancer. They report five-year survivals of 22 percent, 9 percent and 16 percent, respectively. Of note, in one surgical series in which 1,155 explored but unresected patients were followed, there were no five-year survivors.[8] The more frequently recognized Veterans Administration cooperative study, which showed only a very modest survival benefit from primary radiation therapy, is essentially noncontributory to this question because of inadequate technique by today's standards (a third received less than 4,000 rads tumor dose and 90 percent were treated with orthovoltage) and unfavorable patient population (20 percent actually died before the completion of radiation therapy). Despite their misleading conclusion as stated in their abstract "Radiotherapy did not prolong survival," there was actually no discussion of this most cogent issue in the report from Travis Air Force base.

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* * *

The Authors Reply:

To the Editor: Our study is obviously open to criticism regarding certain specifics concerning the analysis and management of lung cancer. We think that our statistical data regarding survival are reasonably accurate. The subdivision of stage III into stages III and IV appears to be justified. The two

components of the survival curves also seem to be valid observations that will be useful in the analysis of potential treatment programs.

The issue regarding the value of radiotherapy in lung cancer is indeed a hotly contested one. It would have been wise, on our part, to have omitted this from our analysis, since it does little to settle the issue. Retrospective studies such as these are undoubtedly filled with bias. We were careful in our conclusions since we recognized that such bias could have occurred compounded by the relatively small number of cases. Careful analysis of the published graphs shows that there may have actually been some advantage to the radiotherapy treated group depending on the interpretation desired. This advantage is relatively small and of no statistical significance.

The issue of the value of radiotherapy in lung cancer will not be resolved for several years. Nearly all proponents seem to agree that the relative merits are currently measured in weeks of survival rather than in years which would be required to make this issue worthy of the energy spent in debating it. We must stand on our data and regret that it may appear to be misleading to some. Additional prospective studies of this issue are needed to satisfactorily resolve it.[1] It may well be that the issue at hand is not one of local disease control, but that of the presence of micrometastasis at the time of the initial evaluation.

In the meantime, there is no valid reason to withhold radiotherapy as part of the standard treatment of lung cancer. The decision regarding such therapy will continue to be that of the individual treatment center. There is no doubt about the merits of initial tumor response to radiotherapy. The high failure rate may be due to any one of several factors. Physicians should be encouraged to continue to refer patients to large treatment centers for investigation and therapy. Likewise, treatment centers must continue their refinement of patient selection through accurate staging procedures, and improve and standardize therapy through prospective trials designed to take advantage of current knowledge and past experiences.

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Outpatient Cardiac Catheterization

To the Editor: Justifiable concern has been expressed in recent years over the rising cost of health care in general, and in particular over the cost involved in the nation's largest single health problem, coronary artery disease. Growing acceptance of coronary angiography has led to its widespread use as a procedure. Careful patient selection is of primary importance in eliminating the costs of unnecessary studies. In addition, attempts should be made to control the cost of the procedure itself by discouraging the rote retrieval of superfluous data during the routine study (that is, routine right heart catheterization, die curves and the like) and by avoiding costs of unnecessary hospital admissions at the time of study.

In this regard, we would like to mention our experience in carrying out elective outpatient cardiac catheterizations as an important contribution toward controlling the overall cost of the procedure. In reviewing approximately 5,000 elective cardiac catheterizations done at Daniel Freeman Memorial Hospital, it became apparent that late complications of cardiac catheterization are rare and can be predicted at the time of study.[1] Based on this experience, outpatient catheterization has been done by the brachial approach on 537 patients at Daniel Freeman Memorial Hospital over the past three years. Of these patients, 350 were outpatients whose physical condition was deemed stable by recent office evaluation. While 25 of these patients were admitted to the hospital following catheterization for observation (usually because of severe coronary artery disease found at catheterization), the remainder were observed for three hours following the procedure and subsequently allowed to return home. During this observation period they were

fed a meal and were ambulated, and serial checks of the radial pulse were done. There were no late complications. A single patient had a weak radial pulse on leaving, and he returned the following day for a successful thrombectomy procedure.

Outpatient cardiac catheterization was done in an additional 187 patients, transfers from hospitals in the vicinity. These were generally patients admitted for accelerated angina or subendocardial infarction in whom cardiac catheterization was required during their current admission. Of this group, 20 patients remained at Daniel Freeman Memorial Hospital to undergo coronary bypass procedures. The remainder returned by ambulance to their original hospital after a short period of observation. No major catheterization-related complications were noted. In two patients a weak radial pulse developed and successful thrombectomy was carried out at the referring hospital on the following day.

This experience is being combined with that of the few major catheterization laboratories from other parts of the country where outpatient catheterization is done. Preliminary data in a collaborative study of more than 4,000 outpatient cardiac catheterizations are similarly favorable and will be reported in the future. The safety of this approach to cardiac catheterization should thus be established, and outpatient studies are likely to have an important financial impact on the overall cost of cardiac catheterization. Outpatient catheterization can reduce costs by as much as 40 percent of that of the usual inpatient study. Additional benefits of the outpatient approach include better patient acceptance and comfort.

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A Monumental Squeak

To the Editor: All of us who have served on review or utilization committees have wondered what in the name of sense we were doing. Like sheep, hounded by the baying of the federal sheep dogs, we have followed blindly, protesting only by some mild bleating. As doctors we should long ago have been demanding the same answers that we require of any new medical or surgical procedure: Does it work? What are its side effects? What does it cost the patient?

Are Utilization Committees Effective?

In New York, Cornell University Medical Center has for years attempted diligent utilization review and audit. A critical examination of the results is startling and terrifying. An investigator at Cornell has shown that over the years an average of 9,500 hospital records were reviewed annually to identify *six* patients per year who were in the hospital too long. The cost of identifying *each* of these patients was $34,212.[1] Extrapolating the expense of the program at Cornell to national proportions implies a cost estimated to exceed the entire research budget of the National Institutes of Health.

Again extrapolating from the Cornell experience, the work load for physicians would require the full-time professional output of six times the entire graduating class per year at Cornell.

In three years the "guidelines" for implementing the program have grown from 3 pages to 26 pages, and the nonmedical staff now requires 20 people working full time. On a national level this would require a cadre of thousands.

Well, is there a subtle influence on physicians who, knowing that a utilization review panel is overseeing hospital stays, thereby tend to decrease hospital use? Not at Cornell. There was no evidence that the implementation of utilization review had any effect on the length of stay, which remained roughly the same throughout the entire period of the study.

Does a Medical Audit Improve Hospital Medical Care?

Hundreds of us have attempted over the years to respond to the mandate of the Joint Commission on Accreditation of Hospitals (JCAH) by setting up ideal standards of care for individual diseases from asthma to Zollinger-Ellison syndrome—including such intangibles as how often to take blood pressure, when and how often to measure blood gases and whether to obtain a chest x-ray. Most of us have reacted with the same skepticism that Rembrandt might have felt if the Dutch government told him how to mix his paints. But under the combined threat of non-

compliance with Professional Standards Review Organizations (PSRO) legislation and the JCAH, we have done our best. As we labor most of us have become frustratingly aware that this system cannot work, will not work and is not in the best interest of patients. However, in the United States no matter how ridiculous a situation is, it is not acknowledged to be until the point is made in print. The Mayo Clinic, using bacterial cystitis as the model disease, could find "no improvement in patient care from strict adherence to the treatment ideals set forth by the audit committee."[2] If cookbook medicine doesn't work in the relatively uncomplicated situation of outpatient treatment of acute cystitis, how can anyone possibly believe that it is realistic to set up a cookbook pattern for the treatment of diabetic ketoacidosis complicated by heart failure and pneumonia? Can there really be a road map for the appropriate treatment of peptic ulcer complicated by thrombophlebitis? Even to imagine so, seems to me to be schizophrenic.

At Cornell, 15 audits over two years (at a cost of $71,821) were received by the medical staff with "almost total indifference." "It did nothing to alter the type or quality of medical behavior."

At last, we are documenting and publishing what almost all of us have felt intuitively for years. Utilization review is a monstrous mistake requiring the expenditure of hundreds of thousands of dollars and consuming the productivity of thousands of physician work hours for very minimal (if any) improvement in the efficiency of hospital utilization or in savings in hospital costs.

Medical audit has similarly shown what we also sensed: You cannot teach Michelangelo to paint by the numbers and hope to improve the quality of his painting.

Once again legislation has labored to produce an elephant and has brought forth not even a mouse—only a monumentally expensive squeak.

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Correction: Anastomosis

To THE EDITOR: I am discouraged that your excellent editorial policy overlooked the repeated misspelling of the word "anastomosis" on pages 384 to 387 of the November issue [Wolfe JD, Simmons DH: Hemoptysis: Diagnosis and management. West J Med 127:383-390, Nov 1977]. The article, otherwise, was an excellent review of the subject of hemoptysis.

The word is derived from the Greek words "ana" and "stoma," and literally when one joins two tubular structures together they are joined mouth to mouth. Excuse my nitpicking, but how can we get the house officers to spell correctly when the highly regarded journals don't? Or, maybe by the same token, it doesn't matter any more.

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ED. NOTE: You are so right—and it *does* matter. Thanks.

Refer to: Cordes SM: Factors influencing the location of rural general practitioners—A study in Washington state (Health Care Delivery). West J Med 128:75-80, Jan 1978

Factors Influencing the Location of Rural General Practitioners

A Study in Washington State

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Data on (1) personal background, (2) place of medical education and training, (3) reasons for selecting the present place of practice and (4) previous practice location were gathered and analyzed from 41 general practitioners in rural Washington state. The analysis was done to isolate factors influencing the choice of location by physicians.

Results show that most of the physicians had spent at least some of their preadulthood years in small communities and that most had some exposure to the state of Washington before establishing their practices in the state.

In addition to the apparent importance of previous exposure to small communities and Washington state, the physicians were also influenced in their locational choice by (1) the professional advantages or appeal of the community, (2) recruitment efforts by persons within the community and (3) economic reasons.

The physicians were rather immobile. Most had never practiced in another community and only two of the 41 physicians planned to move to another community.

POLITICIANS AND OTHERS involved in forming health care policy are continually expressing concern over the availability and accessibility of medical care services in rural areas.[1-16] The National Health Service Corps, a variety of loan forgiveness programs, rural preceptorship programs, the Indian Health Service and the Hill-Burton program are just some of the manifestations. Of particular concern is the fact that the distribution of physicians is highly skewed in favor of urban areas. In 1973 the nation's most urban counties (counties in Standard Metropolitan Statistical Areas with 5,000,000 inhabitants or more) had approximately five times as many active, nonfederal medical doctors in patient care per 100,000 population as did the most rural counties (nonmetropolitan counties with less than 10,000 inhabitants).[17] The success of such policies and programs as the National Health Service Corps and the various loan forgiveness programs is dependent upon isolating and thoroughly understanding those factors influencing physician location and distribution. Although a considerable amount of work has been directed toward gaining a better understanding of these factors, much additional research is needed. In view of this need,

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the major objective of this article is to report empirical findings dealing with factors influencing physician location.

Methods

During the three years from 1971 through 1973 a study was undertaken in the state of Washington to, first, isolate certain characteristics, attitudes and opinions of a sample of rural general practitioners and, second, determine if any differences in physician productivity exist among different sized rural practices. Although this article focuses on the first of these two objectives (see references 18 and 19 for findings related to the second objective), it should be noted that meeting the second objective resulted in a sample of rural physicians that included a very small number of solo practitioners and a disproportionately large number who were in group practices.

The physicians included in this study were selected from a master list of all physicians in the state of Washington. This master list was supplied by the Washington Medical Education and Research Foundation, and also included all physicians' addresses, which made it possible to identify those physicians practicing in rural communities. A rural community was defined as a place of 10,000 population or less which was not part of a larger population center. Physicians practicing in rural communities were categorized according to the number of physicians in their practice. Practices staffed by anyone other than general practitioners were eliminated from consideration and an attempt was made to enlist the cooperation of a sample of the remaining practices. Cooperation was received and data gathered from a total of 17 practices. Five of these practices were solo practices and the remaining 12 evenly divided among groups of two, three and four physicians.

The 12 counties in which the practices were located had only 87 medical doctors in patient care per 100,000 population. This was well below the national and Washington state average of 130 and 131 medical doctors in patient care per 100,000 population, respectively.[17] The average distance of the 17 practices to a Standard Metropolitan Statistical Area was 69 miles.

In addition to productivity data, the 41 general practitioners associated with the sample of 17 practices were personally interviewed to gather data on their (1) personal background, (2) place of medical education and training, (3) reasons for selecting the present place of practice and (4) previous practice location.

TABLE 1.—*Occupations of Physicians' Fathers*

*Father's Primary Occupation**	*Number*	*Percent of Total Sample (N=41)*
Physicians, dentists and pharmacists	7	17
Other professional, technical and kindred workers	10	24
Managers, officials and proprietors (except farm)	8	20
Farm laborers and foremen, farmers and farm managers	7	17
Craftsmen, foremen and kindred workers	6	15
Sales workers	3	7

*The census lists five additional occupational categories. They are (1) clerical and kindred workers, (2) service workers except private household, (3) operatives and kindred workers, (4) laborers except farm and (5) private household workers. None of these occupations had been pursued by the physicians' fathers.

Findings

Each physician interviewed was asked to specify his father's primary occupation. The United States Bureau of Census' occupational categories provided the basis for classifying these responses. One modification of the census format was to separate the occupations of physician, dentist and pharmacist from other types of professional workers. This was done to determine whether or not there was a tendency for physicians to come from families where the father was directly involved in the delivery of medical care. Such a tendency appears to hold in that 17 percent of the doctors studied had fathers who were either physicians, dentists or pharmacists (Table 1). This percentage, of course, is much larger than the percent of physicians, dentists and pharmacists in the general labor force. Another interesting observation was that 61 percent of the doctors' fathers were either physicians, dentists, pharmacists, some other type of professional or technical worker, managers, officials or proprietors. Only a relatively small portion of the nation's labor force is or ever has been in these occupational categories—categories that also happen to be commensurate with a relatively high socioeconomic status. This suggests that a disproportionately large number of the physicians, in this study came from family backgrounds characterized by relatively high socioeconomic status.

Several studies indicate that a tendency exists for physicians to practice in the same size com-

TABLE 2.—*Places of Residence Before Physician's 18th Birthday*

Population and Location of Community	*Number**	*Percent of Total Sample (N=41)*
Population of Community†		
Less than 2,500	15	37
2,500-9,999	15	37
10,000-24,999	4	10
25,000-49,999	2	5
50,000-99,999	2	5
100,000 and over	12	29
Unclassified responses‡	10	24
Location		
Washington	20	49
States other than Washington	22	54
Foreign countries	7	17

*Column total is more than the sample size due to more than one place of residence for some physicians.

†Based on official census figures for the decennial year closest to the physician's birth year plus nine years.

‡Primarily foreign places of residence.

TABLE 3.—*Location of Medical School, Internship and Residency*

	Medical School		*Internship*		*Residency*	
Location	*Number*	*Percent of Total Sample (N=41)*	*Number*	*Percent of Total Sample (N=41)*	*Number*	*Percent of Those With Residency Training (N=16)*
Washington	4	10	17	41	4	25
Oregon	8	20	6	15	2	12
Other states	22	54	10	24	5	31
Foreign countries	7	17	4	10	5	31
No response	0	0	4	10	2	12

*Two physicians served residencies in more than one state.

munity in which they spent their preadulthood years.[20-34] Before their 18th birthday, 74 percent of the physicians in this study had lived in places of less than 10,000 population, a population category comparable to the size of the place where they were presently practicing (Table 2). Of course it can be hypothesized that 74 percent or more of urban physicians similar in age to the physicians in this study had also lived in places of less than 10,000 population before their 18th birthday. Bureau of the Census data were used to provide a crude test for this hypothesis and the data do not support the hypothesis. At least the percent of *all* persons residing in places of less than 10,000 population was well below 74 percent between census years 1910 (the oldest physician in the study was born in 1903) and 1950 (the youngest physician in the study was born in 1939). More specifically, the percentage of all persons residing in places of less than 10,000 population decreased steadily from 63 percent to 46 percent between 1910 and 1950.[35] In other words, data from this study support the notion that a strong relationship exists between the size of community lived in during preadulthood years and the size of community in which the physician established his or her practice.

A number of studies suggest that a strong correlation exists between the state or region in which a physician is practicing and the state or region in which he or she (1) lived during preadulthood, (2) attended medical school and (3) served internship or residency.* Results of this study generally support these findings. Of the 41 physicians in the study, 26 had had some previous exposure to Washington state by living there during preadulthood, attending medical school in Washington, or serving their internship or residency in Washington (or a combination of these). Washington accounted for almost as many places of residence before age 18 as did all other states combined (Table 2). On the other hand, only four of the 41 physicians had received their MD degree from the University of Washington, the state's only medical school (Table 3). Part of the reason for this unexpectedly small number is that 19 of the 41 doctors had graduated from medical school before 1950, the year in which the University of Washington graduated its first class of medical students. It was found that 20 percent of the sample had graduated from medical school in neighboring Oregon.

Although only 10 percent of the doctors were graduates of the University of Washington Medical School, 41 percent had served their internship in Washington (Table 3). This figure was greater than for all other states combined. Sixteen of the doctors had had some residency training. As with internship, more of the residencies had been served in Washington than in any other state. In both cases (that is, location of internship and residency) neighboring Oregon was a distant second.

The reasons given by physicians for choosing to practice in their present community are presented in Table 4. By far the most frequently cited reason—"personal preference for the general area and/or this type community"—was mentioned by 71 percent of the physicians. "Per-

*References 21, 22, 24, 27, 33, 34, 36, 37-41

TABLE 4.—*Reasons for Choosing to Practice in Present Community*

Reason Given	*Number**	*Percent of Total Sample (N=41)*
Personal ties to the community	7	17
Personal preference for the general area and/or this type community	29	71
Professional appeal of the community	15	37
Recruited by individuals within the community	12	29
Economic reasons	16	39
Other reasons	4	10

*Column sums to more than the sample size due to multiple responses by some physicians.

sonal ties to the community" was mentioned by 17 percent. This reason differed from "personal preference for the general area and/or this type community" in that it had reference to family and childhood attachments to the particular community in which the physician was presently practicing. These type attachments have been found to be important in other studies.*

These two reasons—"personal preference for the general area and/or this type community" and "personal ties to the community"—for choosing a particular practice location reinforce the earlier argument that a tendency exists for physicians to practice in the same state or region in which they lived during preadulthood, attended medical school, or served their internship or residency. Specifically, many of the responses categorized under "personal preference for the general area and/or this type community" and "personal ties to the community" indicated that the physician had had previous exposure to the general area or community in which he was currently practicing. In many cases this exposure occurred during preadulthood, while attending medical school, or during internship or residency training.

In choosing their present practice location, 37 percent of the physicians were influenced by the "professional appeal of the community" (Table 4). Although such a finding does not necessarily suggest rural areas are as professionally attractive as urban areas, it does suggest that rural areas have at least some professional appeal. However, the professional appeal or advantages of rural areas is rarely mentioned in the popular or professional literature. On the other hand, the alleged disadvantages of rural practice are constantly being stressed[5,11,14,43-47] which may be giving medical students and nonrural physicians an image of rural practice—at least rural *group* practice—that is *unrealistically* negative. Moreover, many of the professional factors in which rural areas are at a disadvantage (for example, limited specialized facilities) have been shown to be relatively unimportant for primary care physicians[48-51]—the type of physicians rural areas typically need. Among the specific responses categorized as "professional appeal of the community" were: "hospital was nearby," "an opportunity for group practice existed" and "rural practice provides more satisfaction and independence."

The location decision for 29 percent of the physicians included the fact they were "recruited by individuals from within the community." Although the popularized literature occasionally suggests the need for recruitment efforts,[52] the more scholarly research and literature rarely mention the effect of such efforts. Heretofore, these efforts may have been underestimated in terms of their importance. For example, only recently the Indian Health Service discovered that two potent recruitment tactics are personal visits to potential recruits and bringing potential recruits onto Indian reservations to give them an opportunity to make their own observations.[53] Such strategies are particularly important if nonrural physicians and medical students do, in fact, have an unrealistically negative image of rural practice as was suggested earlier, and if recruitment efforts are successful in creating a more realistic image.

The above four reasons for choosing a practice location—"personal preference for the general area and/or this type community," "personal ties to the community," "professional appeal of the community" and "recruited by individuals from within the community"—are noneconomic in nature. However, such economic reasons as "the opportunity to acquire a financially sound practice" were mentioned by almost 40 percent of the doctors as a factor influencing their location decision. The more frequent mention of noneconomic, as opposed to economic, factors is consistent with other studies that suggest both types of factors are important but that noneconomic ones prevail in the locational decision.*

The data in Table 5 are consistent with results of other studies[20,27,30,34,57] in that the data suggest physicians are relatively immobile. For example,

*References 7, 20, 22, 24, 29, 30, 34, 38, 42

*References 20-24, 27, 30, 32, 34, 42, 54-56

TABLE 5.—*Years in Present Community and Plans for Future Relocation*

	Number	Percent of Total Sample (N=41)
Number of Years Practicing in Present Community		
5 years or less	5	12
6-10 years	6	15
11-15 years	6	15
16-25 years	18	44
More than 25 years	6	15
Do You Plan to Continue Practicing in Your Present Community?		
Yes	35	85
No	4	10
Uncertain	2	5

TABLE 6.—*Number of Communities in Which Physicians had Practiced*

*Number of Communities in Which Physicians had Previously Practiced**	Number	Percent of Total Sample (N=41)
None	22	54
One	11	27
Two	6	15
Three	2	5

*Excludes practice locations during internship, residency, and time spent in the armed forces.

59 percent of the physicians interviewed had been practicing in their present community for more than 15 years. Furthermore, when asked whether they planned to continue practicing in their present communities only four said they did not, and two of these were simply planning to retire from active practice. The apparent tendency for doctors to remain in a particular community is further underscored by data in Table 6. Of the respondents, 54 percent had never practiced anywhere other than in their present community. The 19 doctors who had practiced somewhere else were then asked where they had practiced before. In 16 of the 19 cases it was possible to determine (using Bureau of the Census data) the population of these towns during the time in which the physician had practiced there. Seven of the 16 doctors had practiced only in communities of less than 10,000 population and an additional six doctors had practiced both in communities of less than 10,000 population and communities with population greater than 10,000. Only three of the 16 had practiced only in communities with populations greater than 10,000. This suggests that among the more mobile physicians there was some tendency to practice in communities similar in size to their present place of practice.

Summary and Discussion

Data on (1) personal background, (2) place of medical education and training, (3) reasons for selecting the present place of practice and (4) previous practice location were gathered from 41 general practitioners in rural Washington.

Analysis of the data gives additional support to the presumed importance of the physician's personal background and location of medical education training in selecting a place of practice. In particular, there appears to be a strong correlation between (1) the size of the community in which physicians spend their preadulthood years and the size of community in which they establish their practices and (2) the state in which physicians establish their practices and whether or not they have had any previous exposure to that state.

While the importance of personal background and location of medical education and training appear to be crucial influences in the location decision, other factors are also at work. Among these other factors are (1) the frequently overlooked fact that rural practice—at least rural *group* practice—does have certain professional advantages or appeal, (2) the effects of community recruitment efforts and (3) economic reasons.

In sum, it appears that the optimum strategy for a rural community that can financially support a physician would be to (1) encourage a local person to go to medical school (sons and daughters of local health professionals and other white collar workers apparently need the least amount of encouragement and financial support) in their state, (2) encourage him or her to serve internship and residency training in their community or region, and (3) actively recruit the physician to "return home." Initially securing a physician appears to be the major part of the overall struggle in that most of the physicians in this study were relatively immobile once established in practice. Furthermore, those who were somewhat mobile simply tended to move from one small community to another rather than from a small community to an urban area.

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Medical School Graduates Who Leave California

A Study at the University of California, San Francisco

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A follow-up survey of 1,087 physicians who had graduated from the University of California, San Francisco, School of Medicine from 1951 through 1971 was completed in 1977. A total of 307 (28.2 percent) of these persons were found to have left California. Comparison of the 307 who left with the 780 who remained showed only slight and statistically insignificant differences on most variables, such as sex, academic performance in premedical and medical education, educational level and social class of parents, age at entry into medical school, ratings by admissions interviewers, choice of specialty and a wide variety of personality inventory measures. Among the variables that did differentiate were place of birth, location and prestige of premedical college, preferences for subjects in the sciences and the humanities, and the Medical College Admission Test (MCAT) scores for quantitative ability and general information. However, attempts to combine these individual differentiators into clusters or equations from which to forecast emigration from California were unsuccessful.

CALIFORNIA is ordinarily thought of as a physician-importing state. A survey[1] taken in December 1973 found that of 46,022 California physicians, only 12,572 or 27.3 percent had taken their medical degrees in California schools. The American Medical Association report[2] on medical education in the United States, 1973-1974, noted that of 6,202 internships and residencies offered by California medical facilities only 1,708 or 27.5 percent were filled by graduates of California medical schools. This last figure may be compared with those of 38.7 percent for Pennsylvania, 55.3 percent for Oklahoma, 62.4 percent for Indiana and 73.3 percent for Nebraska.

Another index is afforded by the number of physicians per 1,000 population.[3] Among the larger American cities, Boston ranked first, New York second, San Francisco third and Los Angeles seventh. Yet, California ranked sixth from last among the states in the number of medical school graduates per inhabitant. Physicians in states other than California have noted and commented rather pungently on these differentials. For example, de Vise[3] observed that Illinois educates two to three

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This paper is based on a program of research on medical education, choice of specialty, location of practice and related issues being carried out at the institute under a grant from the Robert Wood Johnson Foundation.

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times as many American doctors as it receives as interns, residents and licensed practitioners, where California educates half as many doctors per inhabitant as Illinois, but receives twice as many interns, residents and physicians.

It appears to be beyond dispute that California schools have trained no more than a third of the physicians who are practicing medicine in the state. What is less widely recognized is that this in-migration is only a part of the picture: there is also an out-migration of a certain number of California trained physicians who leave the state to practice elsewhere. At the Institute of Personality Assessment and Research, University of California, Berkeley, we have been working with a sample of 1,061 men and 134 women who were admitted to the University of California, San Francisco, School of Medicine from 1947 through 1967. Earlier reports on this project have dealt with issues such as specialty preferences,[4] comparison of students from medical and nonmedical families[5] and personality changes among women physicians.[6]

In arranging for a mailing of a follow-up questionnaire in 1972-1973 it was found that a substantial number of the graduates had taken up residence outside California. A systematic check of our returns, medical association records and state licensure listings led to the finding that of the 1,087 persons from our cohort who had taken the MD degree in San Francisco, 307 or 28.2 percent were now situated in out-of-state practices. The fact that an appreciable number of graduates leave California raises the interesting question of whether those who leave might be different in any detectable way from those who remain. A decision was therefore made to examine our research data in regard to this query.

Base Rates

Non-California birthplaces were recorded for 558 of our 1,087 physicians, giving an out-of-state base rate of 51.3 percent. Premedical education was completed in non-California colleges by 193 persons, giving an out-of-state base rate of 17.8 percent. As of the time of our final verification of location in August 1977, 307 of the physicians were in non-California locations, giving an out-of-state base rate of 28.2 percent.

States to which more than 10 graduates had emigrated included Maryland (30), Massachusetts (23), Oregon (20), Arizona (18), Colorado (17), Texas (13), Hawaii (12), New York (12) and Pennsylvania (11). There were five states in which no graduate was located: Arkansas, Delaware, South Dakota, Vermont and Wyoming. Thirteen reported addresses outside of the United States, including one in Canada and two in England.

Findings

Sex

A first analysis was carried out for sex. There were 115 women graduates in our sample, of whom 33 were in out-of-state locations. For the 972 male graduates the out-of-state frequency was 274. The departure rates of 28.7 percent for women and 28.2 percent for men were insignificantly different when evaluated by the chi-square test for the 2×2 table of frequencies.

Place of Birth

Place of birth was considered next. Of the 558 persons who had been born outside of California, 182 left after taking the MD degree. Their departure rate of 32.6 percent is slightly higher than the base rate of 28.2 percent, and the difference is statistically significant at the .01 level when evaluated by the chi-square test.

Premedical College

Location of the premedical college was also significantly related ($p < .01$) to the criterion dichotomy. There were 193 who had attended out-of-state colleges, and for them the departure rate was 40.9 percent. A prestige rating of the premedical college gave similar results. Using a scale proposed by Dawes,[7] ratings on a six-step continuum were assigned to each school. There were 222 graduates who had attended schools with higher ratings, of 4, 5 or 6. Their departure rate was 36.9 percent, significantly ($p < .01$) greater than the base rate of 28.2 percent.

Academic Performance

Attention was also paid to scholastic aptitude and performance in premedical and medical training, and to the kinds of courses liked most. Table 1 presents data comparing those who remained in the state with those who left. The 307 graduates who left the state were more or less indistinguishable from the 780 who remained in regard to premedical academic performance. Similarly, no significant differences were observed in academic performance in medical school. Grades in

TABLE 1.—*Comparison of Medical School Graduates Who Remained In or Left California*

Variables	Remained SRG	Remained SD	Left SRG	Left SD
Premedical Grade Averages				
Overall	3.28	0.33	3.30	0.33
Scientific subjects	3.35	0.39	3.38	0.37
Last two terms	3.34	0.39	3.37	0.39
Courses Liked Best				
Scientific rating	7.06*	2.02	6.78	1.92
Humanities rating	4.84	1.94	5.11*	1.85
Medical College Admission Test Scores				
Verbal	566.49	81.06	573.47	78.29
Quantitative	571.28	77.31	582.09*	77.26
General Information	561.60	79.17	575.66†	74.31
Science	583.01	69.14	590.16	59.77
Medical School Grades				
Year 1	50.23	9.55	50.04	9.35
Year 2	49.87	9.22	50.36	9.85
Year 3	49.98	9.63	50.16	10.23
Year 4	49.99	9.99	50.05	10.12
Cumulative	49.93	9.86	50.09	10.33

SD = standard deviation
SRG = scores, ratings or grades

*Mean higher, $p < .05$.
†Mean higher, $p < .01$.

medical school, it should be explained, are expressed in standard scores with a mean of 50 and a standard deviation of 10, whereas the premedical averages are in the usual form in which A equals 4, B equals 3, and so forth. The conversion for grades in medical school was necessary because of several changes made during the years of the study in the scales used for grading.

Subjects Liked Best

In the biographical inquiry completed by the students when we first saw them a question was asked concerning the three school subjects they liked best. The responses were rated on two scales developed by Goldschmid[5] to indicate an emphasis on either the humanities or the sciences. Values on the Goldschmid scales range from lows of 1.87, for comparative literature and dramatic arts on the science scale, to highs of 10.0, for physics on the science scale and philosophy on that for the humanities. Suppose that an entering student cited biochemistry, zoology and political science as the three subjects liked best. His "science" score would then be the average of the three assigned ratings, 9.8, 9.0 and 4.5, and his "humanities" score would be the average of the three ratings 2.1, 2.7 and 7.2.

The scientific and humanities ratings for subjects liked best both differentiated significantly between the graduates who stayed and left. Those who remained in the state had a slightly higher average on the science scale, whereas those who left had a slightly higher average on the humanities index. There were also very small but statistically significant differences on two of the MCAT scales. The graduates who left the state scored slightly higher on the quantitative and general information measures.

Nondifferentiating Variables

In addition to the variables already discussed there were many others that were analyzed but failed to produce significant differences. For example, the two groups were essentially the same in regard to education and social class of parents, ratings by the admissions committee interviewers and age at entry, and on personality inventory measures such as dominance, social presence, endurance, need:achievement, flexibility and autonomy.

Choice of Specialty

Current specialty was also unrelated to the dichotomy of stay versus leave. A 2×12 contingency table was constructed, pitting the stay-leave classification versus anesthesiology; dermatology; eye, ear, nose and throat (EENT); family medicine and general practice; internal medicine; obstetrics and gynecology; pathology; pediatrics; psychiatry; radiology; surgery, and other or unknown. Departure rates for the larger categories were very close to the base of 28.2 percent for the total sample. For example, there were 211 internists of whom 26.1 percent had left the state; departure rates of 26.0 percent, 28.6 percent and 26.4 percent were observed for surgery, EENT, and family and general practice, respectively. The highest figure was obtained for pathology, where 39.3 percent of the 56 physicians in the specialty had left the state, and the lowest was for obstetrics-gynecology where the rate was only 17.3 percent. In spite of these individual variations, chi-square for the table was only 12.98, which with 11 degrees of freedom had a probability of .29.

Combinations of Variables

No single sign or index showed more than a very slight relationship to the stay-leave dichotomy. The possibility of identifying a simple

combination of individual discriminators must still be examined. A stepwise multiple regression analysis was computed for the seven most promising variables: place of birth, location of premedical college, prestige of premedical college, science rating of subjects liked best, humanities rating of subjects liked best and two MCAT scores. Significant increments in reproducing the 0-1 criterion (stay or leave) were found for only three variables, out-of-state birth, out-of-state premedical college and high-prestige premedical college, each scored on a 0-1 basis. The multiple correlation for these three predictors was only .17, accounting for less than 3 percent of the variance in the stay-leave criterion.

A multiple cutoff analysis was also carried out, again using 0-1 scoring of the various predictors. That is, a value of 1 was assigned for attending a premedical college with a prestige rating of 4, 5 or 6, and a value of 0 for attending a college with a rating of 1, 2, or 3. On MCAT Quantitative, a value of 1 was assigned for scores of 650 or above, and a value of 0 for scores of less than this. A score of 0 or 1 was in this way assigned for each of the seven best differentiators, as listed in the preceding paragraph. This method also failed to produce a clear differentiation. For example, of the physicians with sign scores of 5, 6 or 7, 40.6 percent had left the state whereas 59.4 percent had remained. The rate of departure is significantly greater than the base rate of 28.2; nonetheless, the best prediction to make about persons with scores of 5, 6 or 7 is that they will remain in the state.

Discussion

What may be concluded from this analysis of 307 California-trained physicians who left the state after receiving their medical degrees? One conclusion is that the rate of departure is appreciable, 28.2 percent to be exact. In 1973-1974 the eight medical schools in California awarded 733 MD degrees. If the departure rate of 28.2 percent is accepted as valid, this means the loss of about 207 new physicians from California per year.

A second conclusion is that there are very few systematic differences between the graduates who leave and those who stay. For example, the two groups cannot be distinguished in regard to academic performance in either premedical or medical training, choice of specialty, sex, age at entry into medical school and social class of family, and personality variables such as dominance, autonomy, need:achievement, social presence and flexibility. There were three small but statistically significant differences on background factors. Doctors who left the state had more often been born in out-of-state locations, had more often attended out-of-state premedical colleges and had more often attended high-prestige premedical colleges. On the Medical College Admission Test they had slightly higher scores on general information and quantitative ability, and in their preferences for college subjects they gave slightly more emphasis to the humanities and slightly less to the sciences.

A third conclusion is that accurate forecasts concerning the eventual leaving of the state cannot be made at the time of entry into medical school, even if the differentiating signs just enumerated are combined by means of either multiple regression or multiple cutoff techniques. Significant relationships between the stay-leave dichotomy and clusters of from five to ten predictors were obtained, but at all values of these clusters the number of physicians who remained in the state was substantially greater than the number who left.

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Refer to: Hadley GG, Chrispens JE: Unprofessional physicians—Some correlative data (Medical Education). West J Med 128:85-88, Jan 1978

Unprofessional Physicians — Some Correlative Data

G. GORDON HADLEY, MD, *and* JERE E. CHRISPENS, MA, *Loma Linda, California*

In the background of those physicians who have problems in medical practice serious enough to attract attention by the licensing body, there are factors that apparently can help predict such behavior. As a candidate for medical school the applicant more likely to have future problems has the following profile: (1) older than the average applicant with a lower grade point average; (2) more likely to have used tobacco; (3) did not receive a baccalaureate degree; (4) no military service; (5) turned in a sloppy handwritten application form, and (6) received a less than ideal character reference by the college from which applying. Furthermore, after admission to medical school the person more prone to future problems tends to be a poorer student than his peers and to receive a poorer rating in his first postgraduate year. The Loma Linda University graduate who has had such problems is also more likely to have settled in Southern California and to be in general practice.

IT IS THE CONCERN of every medical school admissions committee to select applicants who will show the greatest promise of success as future physicians. The attributes of most importance are not the cognitive knowledge and academic standing, but rather those that will relate to integrity, empathy and ethical practice. Obviously, the qualities that characterize a good physician are hard to define. Ideally, one would like to have some objective method to evaluate the quality of medical care delivered by the individual graduate in his contact with patients. To our knowledge, no satisfactory comprehensive and objective methods for such evaluation have been devised.

On the other hand, quality of medical practice can be evaluated by observation based on physicians who have shown specific inability to conform to standard medical practice or to ethical society. The present study deals with such a group: those who have been cited by the California State Board of Medical Examiners (now called the Board of Medical Quality Assurance)

Dr. Hadley is Dean of Loma Linda University School of Medicine and Mr. Chrispens is an instructor in Biomathematics, Loma Linda University School of Medicine.

Reprint requests to: G. Gordon Hadley, MD, Office of the Dean, Loma Linda University School of Medicine, Loma Linda, CA 92354.

TABLE 1.—*Types of Offenses in 83 Cases of Disciplinary Action*

Narcotics	19
Narcotics and one of the items below	19
Abortions	8
Felony and moral turpitude, etc.	11
Mental illness	7
Unprofessional conduct, etc.	17
Licensure	1
Licensure problem in another state	1
TOTAL	83

for disciplinary action. These disciplinary proceedings of the Board are a matter of public record. The purpose of this study is to attempt to define those characteristics that might enable an admissions committee to identify the type of person who in later practice is more likely to have professional and personal problems of such a nature as to require discipline. Our study concerns the graduates of the Loma Linda University School of Medicine (formerly called the College of Medical Evangelists). The medical school at Loma Linda was established and is presently operated with specific ethical objectives in mind. The Admissions Committee selects students who, it is hoped, will follow the principles and patterns. The purpose of the school is summarized in the *Bulletin,* which states that not only is the school expected to train people in professional school, but also "to guide in the development of values, revealed in the intellectual, ethical, and humane concerns. To engender and nurture the desire to service mankind in the country and throughout the world."[1]*

The present study includes those physicians cited for unprofessional conduct as indicated by the state disciplinary records of 1947 to 1976. Because medical school records of graduates in the distant past are not complete or easily comparable, we have limited the study to those physicians who have graduated in the classes of 1935 through 1975. A total of 83 physicians who graduated from Loma Linda in 1935 or later have been summoned or mentioned by the Board for hearings on charges of unprofessional conduct. The number of graduates during this same time is 3,927. Of this number 3,624 are alive at the last listing. About 65 percent of the graduates are in the state of California. These 83 cases would generally be of those who are practicing or have practiced in California. The offenses charged cover a number of areas, but the most common is the intemperate use and abuse of narcotics. A breakdown of the offenses from the list published by the Board is shown in Table 1.

Narcotic addiction in physicians is reported to be 30 to 100 times as frequent as in the general population.[2] During a 25-year period, 0.5 percent of all physicians licensed in New York State were reported as addicts to the Bureau of Narcotics Control.[3] In California it has been estimated that 1 to 2 percent of physicians in the state have used narcotics at some time in their career and that about half of the 125 cases that come to the Board each year involve narcotics. Figures of 1 to 2 percent of the physician population coming before respective state boards because of drug abuse have also been reported in other states.[4] For statistical comparison we have used the information for all persons in three classes of physicians graduating during this period: classes which graduated in 1944, 1953 and 1961.[5] This includes not only the data available in the file of a biographic and academic nature but also a careful individual follow-up study of each of these graduates. We have compared the biographical, academic and follow-up information of these standard reference classes with the group of 83 who had Board problems. These have been subjected to statistical analysis, using simple t-tests or chi-square, depending on the attributes studied.

Items of General Biographical Nature

The average age at admission of the reference group is 23.2 whereas those who later had Board problems is 25.6. This was highly significant on the t-test. Comparisons of weight, height and sex had no statistical significance.

Academic and Cognitive Data

Comparisons of college grade point averages showed pronounced statistical differences. The grade point averages of the reference group in all courses, in science courses and in nonscience courses were all above 3.0, whereas these values were about 2.8 for those who had later problems with the Board. The t-test showed the difference to be highly significant in all those categories. On the contrary, the Medical College Admissions Test scores were very similar and showed no statistically significant difference. National Board Part

*Loma Linda University is owned and operated by the Seventh-day Adventist Church organization. Students accepted are expected to conform to the standards practiced by the church. This includes abstaining from the use of tobacco and alcohol.

I scores also showed no significant differences. Of interest was the fact that the Part II Medicine, Gynecology and Obstetrics, Pediatrics and Psychiatry scores did have a statistical significance, being definitely higher in those of the reference group. The scholastic standing of the students in each group over the four years of the medical course proved to be another valid finding. The average class standing of the group with problems with the Board was the 39th percentile. This was also highly significant when subjected to the t-test. In other words, the mean class standing of students who encountered trouble with the Board was significantly lower than that of the other students.

Biographical Information Available to Admissions Committee

Prior Use of Alcohol and Tobacco

Though students who on their applications indicated that they had previously used alcohol had an apparently increased tendency toward later problems with the Board, it was not significant. On the other hand, the use of tobacco before entrance to medical school was statistically related to later problems in practice.

Personal and Family History

The status of marriage, with or without children, on admission to medical school had no significance in relation to future problems. There seemed to be no difference between those whose fathers were professionally trained people and those whose fathers were farmers or other types of laborers. Likewise, whether or not the parents were living, or what the mother's occupation was, had little predictive value for future problems. Home address, birthplace and citizenship failed to show any correlation with future problems.

College History

Those students who attended church-sponsored colleges had less tendency to encounter Board problems than those who attended other colleges. Also, students who changed colleges were slightly more likely to run into future problems than those who spent their entire premedical experience in one college. Those students who were admitted with a bachelor's degree were statistically much less likely to have future problems than those without a degree. In comparison with the amount of premedical work, those who came into medical school with only two years of premedical college work had a much greater tendency to have problems later than those who had completed more college work.

Previous Military Service

It is interesting to note that those students who had had military service before entering medical school were less likely to have problems with the Board than those who had never seen military service.

Application Forms

The application forms were classified as to whether typed or handwritten, also as to the relative neatness. Six categories of neatness were established: (1) typed and neat, (2) typed with less than five mistakes in spelling or grammar, (3) typed and sloppy with six or more mistakes, (4) handwritten but neat, (5) handwritten and with four to nine mistakes, (6) handwritten and very sloppy or with more than ten mistakes. As compared with the reference classes, the group of physicians who later had Board problems had a much greater number who turned in sloppy, handwritten application forms (category 6), and actually much fewer in category 2—that is, typed forms with a modest number of mistakes. In other words, physicians who were up for disciplinary action by the Board were much more likely to have turned in a sloppy, handwritten application form when applying for medical school.

Confidential Recommendation From College

The form sent to many of the premedical colleges has included a number of questions about the personal life of the applicant. These include the faculty's evaluation of the applicant's spiritual impact, his character and his personality, and a general overall performance assessment. The evaluation of personality seemed to have no correlation with future problems. However, those who were noted to have a neutral spiritual impact or were not as highly recommended on character or on general recommendation had a much greater tendency to have future Board problems.

Progress in Medical School

Students who took longer than the four academic years to graduate were more likely to have

future practice problems. Attempts at subdividing the group into delayed graduation due to academic reasons, disciplinary causes, graduate study and so forth, did not provide any significant findings.

Follow-up Information

Internship Rating

For many years, the administration of the school has requested confidential evaluations from the hospital where each graduate has spent his first postgraduate year. The forms request that they be evaluated as exceptional, very good, satisfactory or needing improvement. Those who were merely classified as satisfactory had a greater tendency to have later Board disciplinary problems.

Type of Practice

More general practitioners had problems with the Board than their classmates who entered specialties. The difference was highly significant statistically.

Place of Practice

There was a disproportionate number of those who settled in Southern California who had problems with the State Board. Again, the difference was highly significant.

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Using the Roll Test in a Complicated Pregnancy

DR. ZUSPAN: "The roll test is the aortic renal compression test. You lay the patient on her side and take blood pressure in the upper arm—after the patient has been stabilized—and then roll her on her back. You take the immediate blood pressure reading when she is on her back, wait 3 to 5 minutes and take another blood pressure reading. If the diastolic pressure rises 20 or more, it is a positive roll test. The important reading, I personally feel, is when you immediately roll her on her back, because this is the greatest response of the baroreceptors, and this should measure cardiovascular reactivity better, I believe. . . . If you have a negative roll test, that is important because you can be reassured that in greater than 90 percent of those patients preeclampsia will not develop. And if you do a roll test on every visit of a patient from the 22nd or 24th week of gestation, I can assure you that the red flags will begin to go up, and that if the results are positive, somewhere between 60 and 80 percent of the patients will undoubtedly have either transient hypertension or early pregnancy-induced hypertension, and you can do something about that. So you are identifying and preventing."

—FREDERICK P. ZUSPAN, MD, *Columbus, OH*
Extracted from Audio-Digest Obstetrics and Gynecology, Vol. 23, No. 22, in the Audio-Digest Foundation's subscription series of tape recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Medical Information

Refer to: Hurwitz AL, Owen RL: Venereal transmission of intestinal parasites (Medical Information). West J Med 128:89-91, Jan 1978

Venereal Transmission of Intestinal Parasites

ALFRED L. HURWITZ, MD
ROBERT L. OWEN, MD
San Francisco

THE PREVALENCE OF AMEBIASIS in the United States has been estimated at 5 percent, with higher rates in rural areas, the southern states and in lower socioeconomic segments of the population.[2] Because of the care needed in specimen collection and preservation, and the expertise necessary for evaluation of fixed specimens, no prevalence figures are available for most areas. Despite the fact that endemic amebiasis exists in the United States, improved sanitation techniques have largely eliminated transmission to humans from contaminated food and water supplies. Because of confidence that sanitation will interrupt fecal-oral transmission, physicians often do not pursue a diagnosis of amebiasis in the absence of a history of travel outside the United States. Our experience indicates that this low index of suspicion may be inappropriate when dealing with young sexually active populations.

Patients and Methods

Three male patients were seen during a short period at the San Francisco Veterans Administration Hospital, presenting with diarrhea associated with mixed amebic and giardial infection. There was no evidence of significant medical disease, immunosuppression or recent travel out of the local area. In each case parasites disappeared after treatment but were soon replaced by the same or other species (Table 1). Such apparent resistance was observed after treatment with metronidazole (Flagyl®), diiodohydroxyquin (Diodoquin®), tetracycline and quinacrine (Atabrine®).

Careful review of these patients' histories showed that they had all participated in homosexual oral-perineal contact during their usual sexual encounters. After the risk of ingestion of fecal organisms was explained, these patients altered their sexual behavior. Subsequently, with further medical treatment, parasitic organisms disappeared from their stools and did not reappear during our period of observation.

Discussion

The patients in the present study are similar to those described in earlier reports of sexual transmission of amebiasis.[3,4] Our cases are representative of a large number of local cases of amebiasis, recognized in the past year as venereally transmitted. In 1976 the incidence of reported, laboratory-confirmed cases of amebiasis in San Francisco was 101 as compared with 8 cases in 1970.[5] After epidemiologic evidence confirmed that most of these cases conformed to a venereal pattern of transmission, the San Francisco City and County Health Department distributed information regarding sexual transmission of amebiasis and other enteric diseases to members of the local medical society.[6] In addition, the general public has been informed by a recorded telephone message.*

Although direct genital transmission of amebiasis was not observed in our patients, it may occur. Reports of cutaneous amebiasis of the clitoris,[7] cervix,[8] penis,[8] and anogenital region[9] suggest this mode of transmission. Most genital cases have been reported from tropical regions where amebiasis is anticipated,[8-10] but clitoral amebiasis simulating both condylomata and carcinoma has been observed in the United States.[7] With venereal transmission of amebiasis now recognized in the United States, physicians should bear in mind that condylomatous anogenital lesions refractory to treatment may represent amebiasis.

Venereal transmission has been described with a variety of pathogens, including Shigella,[11] cytomegalovirus,[12] hepatitis B[13] and Entamoeba histolytica.[4] Our cases and the local experience of private and public health physicians suggest that Giardia lamblia is also venereally transmitted.

From the Gastroenterology and Cell Biology Sections, Veterans Administration Hospital, San Francisco, and the Department of Medicine, University of California, San Francisco.

An abstract of this paper was submitted to the 1977 meeting of the American Gastroenterological Association.[1]

Reprint requests to Alfred L. Hurwitz, MD, Gastrointestinal Section (111B), Veterans Administration Hospital, 4150 Clement Street, San Francisco, CA 94121.

*Tel Med Tape #5000 can be heard from 10 AM to 8 PM, Monday through Friday, and 11 AM to 5 PM on Saturday, at (415) 929-0200, San Francisco Lung Association.

Many of the amebae observed in our patients are not usually recognized as pathogenic, although chronic diarrhea has been associated with massive Endolimax nana infection.[14] The great number of cysts ingested during direct oral contact with the perineum may have provoked a greater clinical response than is usually encountered with ingestion of fewer amebae from contaminated food. Alternatively the diarrhea observed in these cases may have been unrelated to the detected organisms, especially since symptoms did not always correlate with stool isolates.

The wide variety of amebae in the stools, the rapid change of species during periods of oral-perineal contact, and the eventual elimination of amebae when such activity was suspended, supports a venereal mode of transmission in our cases. Unfortunately, identification of specific persons as carriers was usually not possible. This was due to the long and variable incubation period of the disease, the high asymptomatic carriage rate and the problem of identifying multiple sexual partners. An exception was the male consort of patient 3, who was also found to have Giardia lamblia, and was treated. In the other two cases epidemiologic correlation with specific behavior patterns adequately confirmed venereal spread.

Although some reports have emphasized homosexual transmission of infectious enteric organisms,[3,11] equal attention must be given to heterosexual patients who practice oral-genital, oral-perineal or oral-anal contact. Recurrent unexplained parasitism, especially with atypical organisms, should raise the possibility of venereal transmission. Only direct and open questioning by physicians will elucidate the mechanism of multiple infections, reinfections or apparent treatment failure. Considering the difficulty of altering human behavior, it would be naive to expect uniform or permanent modification of sexual patterns. However, without education of patients,

TABLE 1.—*Clinical Features of Patients*

Patient	*Age*	*Sex*	*Complaint*	*Organisms Isolated**	*Interval from Prior Stool Specimen*	*Treatment*
1.	41	M	Diarrhea	1. EN, EC	..	1. Metronidazole 750 mg TID ×10 days
			Asymptomatic	2. EN, DF, IB	8 weeks	2. Diiodohydroxyquin 650 mg TID×10 days; Tetracycline 250 mg TID×10 days
			ROUTE OF INFECTION EXPLAINED TO PATIENT			
			Mild diarrhea; ? irritable bowel syndrome	3. None	3 weeks	3. None
2.	31	M	Epigastric discomfort; soft stools	1. EN	..	1. None
			No symptoms reported	2. EN, EC, EHi	2 weeks	2. Metronidazole 750 mg TID×10 days
			ROUTE OF INFECTION EXPLAINED TO PATIENT			
			Asymptomatic	3. None	10 weeks	3. None
3.	29	M	Diarrhea	1. EC, GL	..	1. Quinacrine 100 mg TID×10 days
			Asymptomatic	2. EN, EHa	2 weeks	2. Metronidazole 250 mg TID×10 days; Tetracycline 500 mg TID×7 days
			Soft stools; periumbilical discomfort	3. GL	11 weeks	3. Metronidazole 250 mg TID×10 days
			ROUTE OF INFECTION EXPLAINED TO PATIENT			
			Diarrhea; symptoms much improved	4. IB	3 weeks	4. None
				5. None	2 days	5. None

EN = Endolimax nana
EC = Entamoeba coli
DF = Dientamoeba fragilis
IB = Iodamoeba buetschlii
EHi = Entamoeba histolytica
GL = Giardia lamblia
EHa = Entamoeba hartmani

*Numbers refer to separate sequential stool collections or treatments. No enteric bacterial pathogens were isolated from any patient.

conventional medical treatment is unlikely to succeed in eradicating parasites.

As improved sanitary engineering reduces the frequency of contamination of water and food supplies, venereal transmission may become the major route of endemic spread of amebiasis in developed countries.

Summary

Three white middle-class men, referred for evaluation of refractory diarrhea, were found to have mixed parasitic infections of the digestive tract. No pathogenic bacteria were identified. In each case parasitism persisted after conventional medical treatment, and the infective species frequently changed. No patient had immunosuppression or recent travel out of San Francisco. Careful review of medical and social histories showed that all of the patients had engaged in homosexual oral-perineal contact with multiple partners. After explanation of the likelihood of continuous reinfection from fecal organisms, these patients diminished or suspended their usual sexual behavior; after further medical treatment, parasitic organisms were eliminated from their stools. Recognition of this route of transmission is necessary if reinfection is to be differentiated from treatment failure.

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Increased Operative Risk in Old Age

It is generally accepted that old age alone significantly increases operative risk. This is probably not correct. Those biological factors that allow a patient to survive beyond age 65 without any serious systemic disturbances will probably also allow him to survive major surgical procedures. In a series of 51 consecutively seen patients 75 years old and older in whom biliary tract operations were done (and about whom I reported in 1971), the operative mortality was 8 percent; however, all four patients who died had significant coexisting intra-abdominal malignancies. Carl Moyer, in evaluating the effects of age in operative risks, noted that an older person is as able as a young patient to withstand operative risks. He noted that an older person is as able as a young patient to withstand operations that have a short period of physiologic derangement, but is less able to withstand a prolonged period of physiologic derangement.

—EZRA STEIGER, MD, *Cleveland*

Extracted from *Audio-Digest Surgery*, Vol. 24, No. 8, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles in other journals which they consider to be important. The editors believe these titles together with a brief assessment of the articles are worth publishing for the information of our readers.*

Team Nursing Coverage of Prenatal-Intrapartum Patients at a University Hospital—An Innovation in Obstetric Nursing

Kowalski K, Gottschalk J, Greer B, et al

Obstetrics and Gynecology
50:116-119, Jul 1977

DISCIPLINES: Obstetrics, Nursing

READABILITY: Good, well organized

This is a description of a program initiated at the University of Colorado School of Medicine for the purpose of providing nursing care as a continuum through the prenatal period and on into labor and delivery suite. Two nurses are assigned to each prenatal patient. These on-call nurses identify with the patients and develop a close and comforting relation with them. At first attending physicians felt threatened. Later they recognized this as a valuable expansion of their services to patients. Conceivably, this plan could be adopted by many good-sized hospitals.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Erosion of the Inferior Aspect of the Clavicle in Secondary Hyperparathyroidism

Schwartz EE, Lantieri R, Teplick JG

American Journal of Roentgenology
129:291-295, Aug 1977

DISCIPLINES: Internal Medicine, Radiology

READABILITY: Very good

The clavicle, and especially the conoid tubercle, takes its place with the hand as the most sensitive roentgen index of secondary hyperparathyroidism.

—ROBERT B. ENGLE, MD
Laguna Beach, CA

What Are Physicians For?—Commentary

Carson RA

JAMA
238:1029-1031, Sep 5, 1977

DISCIPLINES: Philosophy, General Practice

READABILITY: Requires careful reading and reflection

The author proposes to "examine a more traditional way of conceptualizing the question, what are physicians for?" He deplores the fact that with increasing technology and with (as he quotes J. H. Knowles) "the medicalization of our society . . . in medical matters, we seem to be doing better but feeling worse." He reminds us that although the treatment of disease may be entirely impersonal, the care of the patient must be completely personal; and that the secret of the care of the patient is in caring *for the patient. An article to read and reread.*

—E. R. W. FOX, MD
Coeur d'Alene, ID

The Biology Actions of Solar Radiation on Skin with a Note on Sunscreens

Poh-Fitzpatrick MB

Journal of Dermatological Surgery and Oncology
3:199-204, Mar/Apr 1977

The Selection of a Sunscreen

Bennett RG, Robins P

Journal of Dermatological Surgery and Oncology
3:205-209, Mar/Apr 1977

DISCIPLINES: Dermatology, Surgery, Radiology, Public Health, Pediatrics

READABILITY: Excellent

These two articles are important with the ever increasing realization that excessive sunlight exposure can produce irreparable damage to fair skin. As public health measures, new attitudes about sunbathing and new practices to counteract those adverse effects (especially for high-risk persons) appear warranted. These two articles tell how to avoid sun damage and give detailed information about sun protective agents currently available.

—REES B. REES, MD
San Francisco

Controlled Trial of Aspirin in Cerebral Ischemia

Fields WS, Lemak N, Frankowski R, et al

Stroke
8:301-316, May-Jun 1977

DISCIPLINES: Neurology, Medicine, Vascular Surgery, Neurosurgery

READABILITY: Good

A double-blind trial of aspirin in 178 patients with carotid transient ischemic attacks (TIA). The data and the conclusions of the authors cannot be easily summarized and require careful reading. Aspirin appears to have a limited place in the treatment of stroke.

—ROBERT A. FISHMAN, MD
San Francisco

Aspirin Intolerance—A Review

Abrishami MA, Thomas J

Annals of Allergy
39:28-37, Jul 1977

DISCIPLINES: All disciplines

READABILITY: Good

An excellent review, not only of "allergy" to aspirin, or the "triad disease" (nasal polyps, asthma and aspirin) but of all related disorders, manifestations and their prevalence. The article is replete with excellent tables. There are 96 references. This is worth reading despite the ultimate summary: The underlying mechanism is unknown.

—NORMAN SHURE, MD
Los Angeles

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

LEGAL ASPECTS OF MEDICAL PRACTICE—Second Edition—Bernard Knight, MD(Wales), MRC Path, DMJ of Gray's Inn, Barrister-at-Law, Reader in Forensic Pathology, Welsh National School of Medicine, University of Wales, Cardiff; Honorary Consultant Pathologist, South Glamorgan Area Health Authority. Longman, Inc., Churchill Livingstone - Medical Division, 19 West 44th St., New York City (10036), 1976. 254 pages, $14.50 (Softbound).

Devoted primarily to forensic pathology (that is, medical matters relating to criminal law), this handbook places considerable emphasis upon forms, procedure and statutory law. Unfortunately, the legal discussion is based wholly on the law of the British Isles, and could seriously mislead American readers.

Information presented on various medicolegal topics —such as abortion, the battered child, alcoholism, poisoning, injury and death due to physical agents, asphyxia and sexual offences—is a concise review of relevant medical aspects for the reader. However, this book is brief and provides little depth in the subject matter. As there are several more complete forensic pathology books by American authors available, *Legal Aspects of Medical Practice* would be a poor choice for American readers.

DAN J. TENNENHOUSE, MD, JD, FCLM
Lecturer in Legal Medicine and
Lecturer in Nursing Law,
University of California, San Francisco;
Assistant Professor of Medical Law,
University of California, Hastings College of Law, San Francisco; and
University of San Francisco School of Law

* * *

ACUPUNCTURE THERAPY—Current Chinese Practice—Second Edition—Leong T. Tan, MD, practicing urologist, San Francisco; Margaret Y.-C. Tan, MS, Acupuncturist, Acupuncture Research Clinic, University of California, San Francisco; and Ilza Veith, PhD, DMedSc, Professor and Vice Chairman, Department of the History of Health Sciences, University of California, San Francisco. Temple University Press, Philadelphia (19122), 1976. 259 pages, $17.50.

The interest in acupuncture in western countries, especially the United States, has been reflected by the large number of publications, both those written in English and English translations of Chinese texts. Many of these publications are not suited for medical readers because they are merely an explanation of traditional Chinese philosophy and religion and give the history of development of acupuncture and other Chinese remedies. Others are written for lay audiences or explain acupuncture in such simplified terms that they have no practical application.

Much has changed since the first edition of this text was published in 1973. The initial enthusiasm by acupuncture advocates that acupuncture is a panacea for all ills has been tempered. At the same time resistance among medical practitioners to the incorporation of acupuncture into the therapeutic armamentarium has also decreased. In the preface of the second edition the authors state "Aspirin is not a cure-all! Nor is acupuncture! Any different approach is misguided, possibly even of questionable ethics." This certainly reflects current medical thinking on the subject.

The major portion of the book is devoted to the technical aspects of acupuncture therapy. Detailed descriptions of acupuncture needles and techniques of needle insertions are extremely valuable. Although these techniques are fairly straightforward, several methods which enable an acupuncturist to carry out his therapy with a minimal amount of patient discomfort are explained. The method used to locate acupuncture points is concise, informative and easily understood. These explanations are accompanied by detailed drawings which enable the reader to easily follow the text. Because of the attention to detail in the written text and diagrams, even the relatively uninitiated are able to locate many acupuncture points without much difficulty and for this reason this text is one of the most useful of the currently available books on the subject.

Several new chapters have been added to the present edition and several original chapters have been rewritten. Information about the legal status of acupuncture, new and expanded information on acupuncture anesthesia, a section on lesser used acupuncture points and expansion of the chapter on auricular therapy are valuable additions. A short chapter on diseases and symptoms amenable to acupuncture therapy describes the general principles involved in the choice of points both in the local area as well as at distant sites. Despite the fact that this section was incomplete in the original book, it has not been updated in the current edition. The selection of acupuncture points for the treatment of specific symptoms is extremely brief and the interested reader would do well to refer to other available English texts.

A major shortcoming of the original work was that the authors chose not to follow the western practice of labeling each point by its meridian name and sequential number. This deficit is somewhat corrected by the inclusion of tables indexing all points on each meridian by meridian name and number. However, in the rest of the text these numbers are not used and extensive cross-checking is necessary in order to fully understand acupuncture point location, therapeutic indications for their use, and the like. Even considering the weak points, the second edition of *Acupuncture Therapy* is an extremely useful one for physicians and other medical practitioners who wish to become more familiar with this technique and perhaps incorporate it into their practice.

ANDREW J. LEWIN, MD
Deputy Director
Hypertension, Detection and Follow-up Program
Cedars-Sinai Medical Center;
Assistant Professor of Medicine
University of California, Los Angeles School of Medicine

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THE HEREDITY FACTOR—Genes, Chromosomes, and You—William L. Nyhan, MD, PhD, with Edward Edelson. Grossett & Dunlap, Inc., Publishers, 51 Madison Ave., New York, NY (10010), 1976. 320 pages, $12.95.

This book is intended for lay persons; most specifically for the patients or parents of patients with genetic diseases. To write such a text, summarizing the modern science of human clinical genetics, is a formidable task which the author undertakes with cheerful optimism. Chapters on the classical history of genetics, Mendelian inheritance, chromosomes and chromosomal diseases, disorders of sex chromosomes, amniocentesis, prenatal diagnosis, population genetics, multifactorial inheritance, treatment, eugenics, ethics and genetic counseling suggest the breadth of content. The book attempts to sweep the reader along, as geneticists have been swept along within the last two decades, from Mendel's pea plants to prenatal diagnosis of Tay-Sachs disease. The detective-story

quality of research studies in families afflicted with genetic diseases is well conveyed, and the excitement of a scientific discovery with immediate application to a family is palpable. Dr. Nyhan scrupulously acknowledges workers and discoveries in a style which presumably will not overwhelm the lay reader, by mentioning the key discovery in an area informally. A marvelous sense of whimsy also pervades the book, and both are well illustrated by the following paragraph:

> Until 1969 the situation was simply that hopeless. But during that year Drs. John O'Brien and Shintaro Okada of the University of California, San Diego, found the molecular defect that underlies Tay-Sachs disease. In the August 15 issue of *Science* they reported that patients with Tay-Sachs disease demonstrated a total absence of an essential enzyme known as hexosaminidase A (or hex A for short), which ordinarily breaks down sphingolipid molecules. This enzyme is essential in preventing the accumulation of GM2-ganglioside, a specific sphingolipid molecule, in brain and other neural tissue. In the absence of hex A the concentration of GM2-ganglioside becomes progressively greater, interfering with normal neurological functioning and ultimately resulting in death. For the proper breakdown of the GM2-ganglioside molecule to occur, one of its end portions, called a hexosamine, must be split off. The enzyme controlling this specific process is, of course, hexosaminidase, or hex A. This fact had been known for some time. What proved puzzling was the observation that hexosaminidase levels in the blood, brain, and other tissues of patients with Tay-Sachs disease seemed perfectly normal. O'Brien and Okada developed a technique for analyzing hexosaminidase that revealed there were two distinct components of the molecule. They designated them A and B. In patients with Tay-Sachs disease the A enzyme was missing. This accounted for the faulty breakdown of GM2-ganglioside. It is one of the more assuring aspects of science among men that the riddle of this Jewish disease was solved by an Irishman and a Japanese.

This paragraph also illustrates one of my major concerns with this book. To whom is it addressed? Do parents of a child afflicted with only one of the 13,500 possible genetic diseases need to know that hexosaminidase is a molecule with subunit structure? Do those whose children do not have phenylketonuria (PKU) gain insight from a discussion of the specific brand names of low-phenylalanine formulas used in Europe and America? And yet, spina bifida and anencephaly, the neural tube developmental defects, which are more common than either Tay-Sachs disease or PKU, are discussed very briefly and no mention is made of prenatal diagnosis utilizing amniotic fluid alpha-fetoprotein determination. I mention these examples merely to illustrate that while *The Hereditary Factor* is not a textbook of genetics and cannot be judged by those standards of detail and completeness, as a "mini-course in genetics" for the layman, it is, albeit marvelously readable and exciting, definitely a graduate level seminar.

ELIZABETH M. SHORT, MD
Assistant Professor of Medicine;
Director, Medical Genetics Clinic
Stanford University

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THE HAND—Diagnosis and Indications—Graham Lister, FRCS, Assistant Clinical Professor of Plastic Surgery, University of Louisville; Consultant Hand Surgeon, University of Louisville Affiliated Hospitals. Longman Inc., 19 West 44th Street, New York City (10036), 1977. 224 pages, $27.50.

Dr. Lister succinctly focuses on the practical issues in diagnosing hand disorders and determining proper treatment. The text is complemented by lucid, well-chosen photographs. He covers his subject under chapter headings: Injury, Reconstruction, Compression, Inflammation, Rheumatoid, Swelling and Muscle Testing. The index is excellent and he includes a valuable bibliography.

This is an important text for all physicians who must evaluate and treat hand problems. For the sake of brevity, it does not cover congenital hand disorders or fractures of the forearm and wrist.

EUGENE S. KILGORE, JR., MD
Clinical Professor of Surgery
Chief, Hand Services, Department of Surgery
University of California, San Francisco

RECENT ADVANCES IN DERMATOLOGY—Number Four—Edited by Arthur Rook, MD, FRCP, Consultant Dermatologist, Addenbrooke's Hospital, Cambridge; Civil Consultant in Dermatology to the Royal Air Force. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 395 pages, $27.50.

The *Recent Advances in Dermatology* series rapidly established itself as a key reference source for practicing physicians. This is the place to find a balanced approach to new information that is clinically relevant. Dr. Rook's experience, knowledge and superior judgment enables him to guide each contributor to meet the mark. Unlike most reference works, most chapters in this book are well constructed, easily read *in toto* as a general orientation.

Volume 4 has 11 chapters. Widespread readership will be found for most. Especially noteworthy are opportunity and skin infection, arthropods and the skin, sweat gland disorders, and topical therapy. All dermatologists and medical libraries will find this an essential series to own; internists, generalists and others will find this the place to start their updates in the dermatologic sciences.

HOWARD MAIBACH, MD
University of California, San Francisco
School of Medicine

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HANDBOOK OF OBSTETRICS & GYNECOLOGY—Sixth Edition—Ralph C. Benson, MD, Clinical Professor of Obstetrics and Gynecology and Emeritus Chairman, Department of Obstetrics and Gynecology, University of Oregon Health Sciences Center, Portland. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 772 pages, $9.50.

The sixth edition of Dr. Benson's *Handbook of Obstetrics & Gynecology* continues in the tradition of its predecessors in being a good pocket reference text for medical students rotating on obstetrics and gynecology. It is quite complete in topics but superficial in content, and as such serves as a resource for students wishing to survey the specialty as well as a handy reference for definitions of terms, procedures or philosophical approaches to problems. It does not have the informational depth to be of value to house officers or practicing physicians and should not be expected to replace reference texts or more detailed textbooks should a student wish to obtain a deeper understanding of a particular aspect of the specialty. As a handbook, however, it is quite up-to-date.

MORTON A. STENCHEVER, MD
Professor and Chairman
Department of Obstetrics and Gynecology
University of Washington
Seattle

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MICROVASCULAR RECONSTRUCTIVE SURGERY—Bernard McC. O'Brien, BSc, MS(Melb), FRCS(Eng), FRACS, FACS, Director, Microsurgery Research Unit, and Assistant Plastic Surgeon, St. Vincent's Hospital, Melbourne; Hunterian Professor, Royal College of Surgeons of England; Kazanjian Professor, New York University Medical Center; Consultant Plastic Surgeon to Royal Australian Air Force and to Mercy Maternity Hospital, Melbourne; Senior Research Fellow, Department of Ophthalmology, University of Melbourne. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 360 pages, $38.00.

This excellent small reference book should certainly be in the library of anyone actively engaged in microvascular surgery. It is also appropriate for resident surgeons interested in becoming exposed to microvascular surgery, and it has in addition a very useful section for a trained surgeon who is planning to set up his own operating unit.

In his preface the author points out the pressing need for the establishment of microvascular surgery centers throughout the world and stresses the necessity for developing a broad clinical work load as well as the facilities for experimental hand-in-hand teaching facilities

in microsurgery. He stresses that the needs of the community will be served only by a team effort. This textbook reflects the author's experience in the operating theater, wards and laboratory over ten years at St. Vincent's Hospital in Melbourne. Acceding to the publisher's request for single authorship at this stage has made it possible to present the St. Vincent's Hospital experience in a very well-integrated manner.

Chapters on the history of the operating microscope and the development of microinstrumentation and microsutures begin the book. They are followed by a chapter on the organization of a microsurgical unit.

The key to microvascular surgery is explored in a small but well organized chapter on the pathophysiology of microvascular occlusions. Basic microvascular technique is next described with clear drawings augmenting the careful photography. It includes a section on the use of anticoagulants and is followed by a chapter on the histopathology of microvascular repairs. This last includes a fascinating section on the scanning electron microscopy of microvascular repair. The use of vein grafts in microvascular surgery is given a separate chapter.

The problems peculiar to anesthesia in microvascular surgery are discussed, the author pointing out that the chief problem is likely to be management of extensive blood loss.

Replantation surgery of limbs and digital replantation surgery are covered in two separate chapters and include protocols for determining the appropriateness of replantation for a particular patient, and the operating-room routine when replantation has been elected. The author points out that replanted hands are more useful and require less rehabilitation than unamputated hands which have suffered severe crushing or burning injuries, but he also cautions that if circulation has been established in the hand without revascularization of any of the forearm muscles, the surgeon should not persist with replanatation and the arm should be amputated. He feels that the main indications for digital replantation are multiple digital injuries and single amputations of the thumb. He cautions that a decision to replant a single complete amputation in any finger, including the index finger requires a special circumstance in an adult. A useful addition here is the section on postoperative complications with their recognition and management.

One stage toe-to-hand transfer is examined with a section clarifying the vascular anatomy of the hallux and second toe. He confirms that loss of toes seems to cause little embarrassment in walking, even when the hallux with its metatarsophalangeal joint is removed.

In the chapter on microvascular free flap and ornamental transfers, the author has, in most of the cases shown, resisted the temptation to use a free flap where a pedicle flap would do as well or better. A particularly good looking result of the repair of the dorsum of the nose following basal cell carcinoma removal in an adult is shown, but one could hardly recommend this method for a surgeon less skilled than the author.

The challenging problems of microlymphatic surgery are discussed and very good results following lymphaticovenous anastomoses in the upper extremity are shown. Microvascular free bone and joint transfers are felt to have significant potential usefulness and free muscle transfers are discussed. A remarkably good result in facial palsy is shown. Microneural and funicular nerve repairs are evaluated, the author agreeing with most other contemporary writers that coaptation of at least some of the funiculae in larger nerves is desirable. Microneural grafting and cable grafting are also discussed. The microsurgery of miscellaneous tubes and structures such as the fallopian tubes and vas are considered. Penile replantation is described, and the possibility of microvascular techniques in orchiopexy of the undescended testis is suggested. Experimental colon and small bowel transfers with microvascular anastomoses in dogs suggest another method for esophageal replacement. Microrenal transplantation in rats is presented as a useful research tool and coronary artery surgery is discussed briefly.

Textbooks presented by British publishers are well known for their clarity of writing and as such are a delight to the student. This book is no exception to that observation. For anyone considering work in microvascular surgery, it is well worth its asking price.

RICHARD L. DAKIN, MD
Greenbrae, California

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CLINICAL ORTHOPAEDIC EXAMINATION—Ronald McRae, FRCS, Consultant Orthopaedic Surgeon, Southern General Hospital, Glasgow; Honorary Clinical Lecturer in Orthopaedics, University of Glasgow; Lecturer in Surgery and Orthopaedics, Glasgow School of Occupational Therapy; Lecturer in Anatomy, Glasgow School of Chiropody; Fellow of the British Orthopaedic Association and Member of the Institute of Medical and Biological Illustration. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York Cty (10036), 1976. 219 pages, with original drawings by the author, $11.50 (softbound).

This is a clear and concise, well written and illustrated book for orthopedic examination. It very well supplements the early teaching and experience of students, which may be lacking because of the unfortunate size of student classes and the dearth of adequate clinical material. Students, therefore, may have acquired only a sketchy knowledge of physical examination techniques for various conditions and the book offers a big help in developing procedures for arriving at diagnosis and treatment.

The author has divided the text according to anatomical areas, in so far as patients generally describe their complaints on an anatomical basis. He stresses that such an approach may not reveal the most obscure and hence will tax the most experienced, but the most frequent mistake is failure to diagnose the common. He wisely, in my opinion, has avoided excess details but gives specific and pertinent details for the common problems and advises consulting with recognized orthopedic textbooks for the more demanding readers seeking complete descriptions.

The illustrations are excellent anatomical drawings and point out important features dealing with inspection, palpation and examination of movements, both normal and abnormal, of specific joints and areas. Simple screening tests for such motions are included. There are excellent drawings showing segmental sensory nerve supply as well as motor supply for both upper and lower extremities. Radiographic drawings also are well done, showing numerous common abnormalities of injury and disease.

The final section shows radiographs of common pathological conditions in the segmental areas and is in the form of a diagnostic quiz with some history, important clinical findings for each case and answers given after.

I can highly recommend this book, especially for medical students, interns and residents. It also offers a quick review of clinical orthopedic examination for practicing physicians and surgeons.

PAUL E. McMASTER, MD
Clinical Professor, Orthopaedic Surgery
University of California, Los Angeles
Senior Consultant, Orthopaedic Surgery
Veterans' Hospital, Los Angeles
Senior Attending Orthopaedic Surgeon
Orthopaedic Hospital, Los Angeles, and
St. John's Hospital, Santa Monica

in memoriam

Bailey, William Ellery, Los Angeles. Died October 25, 1977 in Los Angeles, aged 80. Graduate of the State University of Iowa College of Medicine, Iowa City, 1925. Licensed in California in 1927. Dr. Bailey was a member of the Los Angeles County Medical Association.

Bermudez, Diego, Morgan Hill. Died October 30, 1977 in San Jose of heart disease, aged 62. Graduate of Facultad de Medicina Universidad Central de Venezuela Diudad Universitaria, Caracas, 1940. Licensed in California in 1952. Dr. Bermudez was a member of the Santa Clara County Medical Society.

Bonfiglio, Vincent, Los Angeles. Died September 9, 1977 in Torrance, aged 82. Graduate of the University of Maryland School of Medicine, Baltmore, 1921. Licensed in California in 1921. Dr. Bonfiglio was a retired member of the Los Angeles County Medical Association.

Brewer, A. Frank, Merced. Died October 23, 1977 in Merced of hyperglycemia and heart disease, aged 74. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1935. Licensed in California in 1936. Dr. Brewer was a member of the Merced-Mariposa Medical Society.

Buchbinder, Egon, Castro Valley. Died October 23, 1977 in Castro Valley of heart disease, aged 65. Graduate of Medizinische Fakultät der Universität, Wien, 1936. Licensed in California in 1941. Dr. Buchbinder was a retired member of the Alameda-Contra Costa Medical Association.

Burwell, Lorus C., Los Angeles. Died June 15, 1977 of heart disease, aged 79. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Dr. Burwell was a member of the Los Angeles County Medical Association.

Bushnell, John W., Fresno. Died December 2, 1977 in Fresno, aged 69. Graduate of State University of Iowa College of Medicine, Iowa City, 1933. Licensed in California in 1962. Dr Bushnell was a member of the Fresno-Madera Medical Society.

Castles, Charles C., sr., Hanford. Died September 13, 1977 in Hanford, aged 65. Graduate of the University of Tennessee College of Medicine, Memphis, 1934. Licensed in California in 1953. Dr. Castles was a member of the Kings County Medical Society.

Conkling, Charles M., Escondido. Died March 10, 1977 of heart disease, aged 92. Graduate of Tulane University School of Medicine, New Orleans, 1913. Licensed in California in 1923. Dr. Conkling was a member of the Los Angeles County Medical Association.

Firestone, Fred, San Francisco. Died November 10, 1977 in Laguna Hills, aged 82. Graduate of Rush Medical College, Chicago, 1920. Licensed in California in 1922. Dr. Firestone was a member of the San Francisco Medical Society.

Galbraith, Harold, Fullerton. Died November 13, 1977 in Los Angeles of heart disease, aged 68. Graduate of the University of Southern California School of Medicine, Los Angeles, 1937. Licensed in California in 1937. Dr. Galbraith was a member of the Orange County Medical Association.

Goss, Donald A., Eureka. Died November 4, 1977 in Eureka, aged 43. Graduate of Harvard Medical School, Boston, 1959. Licensed in California in 1975. Dr. Goss was a member of the Humboldt-Del Norte Medical Society.

Harrington, John T., San Francisco. Died November 3, 1977 in San Francisco, aged 75. Graduate of the Creighton University School of Medicine, Omaha, 1925. Licensed in California in 1926. Dr. Harrington was a member of the San Francisco Medical Society.

Horn, Paula M., Los Angeles. Died October 4, 1977 in Los Angeles, aged 69. Graduate of the State University of Iowa College of Medicine, Iowa City, 1932. Licensed in California in 1933. Dr. Horn was a member of the Los Angeles County Medical Association.

Hubenka, Albin H., San Diego. Died November 8, 1977, aged 76. Graduate of the Creighton University School of Medicine, Omaha, 1927. Licensed in California in 1947. Dr. Hubenka was a member of the San Diego County Medical Society.

Irvine, Richard B., Concord. Died June 10, 1977, aged 55. Graduate of the University of Southern California School of Medicine, Los Angeles, 1950. Licensed in California in 1950. Dr. Irvine was a member of the Alameda-Contra Costa Medical Association.

Kelley, Donald T., La Mesa. Died November 22, 1977, aged 59. Graduate of the University of Nebraska College of Medicine, Omaha, 1944. Licensed in California in 1952. Dr. Kelley was a member of the San Diego County Medical Society.

Kieraldo, John Henry, jr, Palo Alto. Died October 27, 1977 in Palo Alto of cancer, aged 48. Graduate of the University of Wisconsin Medical School, Madison, 1956. Licensed in California in 1957. Dr. Kieraldo was a member of the Santa Clara County Medical Society.

LOMAS, MAX I., Los Angeles. Died October 17, 1977 in Los Angeles, aged 68. Graduate of the University of Southern California School of Medicine, Los Angeles, 1935. Licensed in California in 1935. Dr. Lomas was a member of the Los Angeles County Medical Association.

MARINOFF, RAYMOND GEORGE, Oakland. Died November 10, 1977 in Santa Rosa of heart disease, aged 53. Graduate of the University of Wisconsin Medical School, Madison, 1952. Licensed in California in 1953. Dr. Marinoff was a member of the Alameda-Contra Costa Medical Association.

MONAHAN, JOHN R., Oxnard. Died May 30, 1977, aged 63. Graduate of St. Louis University School of Medicine, 1939. Licensed in California in 1940. Dr. Monahan was a member of the Ventura County Medical Society.

NAEGELI, ARNOLD E., Newport Beach. Died March 13, 1977 of septal myocardial infarction, aged 73. Graduate of Marquette University School of Medicine, Milwaukee, 1928. Licensed in California in 1932. Dr. Naegeli was a retired member of the Orange County Medical Association.

PULFORD, DELOS SCHUYLER, Sacramento. Died October 26, 1977 in Milan, Italy of injuries received in a fall, aged 85. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1917. Licensed in California in 1926. Dr. Pulford was a retired member of the Sacramento County Medical Association.

ROSE, JACK MORTON, Santa Rosa. Died November 8, 1977 in San Francisco of heart disease, aged 61. Graduate of Northwestern University Medical School, Chicago, 1940. Licensed in California in 1949. Dr. Rose was a member of the Sonoma County Medical Association.

RUETMAN, HENN M., Long Beach. Died October 21, 1977, aged 56. Graduate of Eberhard-Karls-Universität, Medizinische Fakultät Tübingen, Württemberg, 1949. Licensed in California in 1955. Dr. Ruetman was a member of the Los Angeles County Medical Association.

SANDOR, ANDREW A., Orange. Died November 19, 1977 in Los Angeles, aged 64. Graduate of the University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1944. Dr. Sandor was a member of the Orange County Medical Association.

SARGENT, WILLARD S., San Diego. Died November 8, 1977 in Sun City, aged 82. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1920. Licensed in California in 1925. Dr. Sargent was a retired member of the San Diego County Medical Society.

VONKOMAROMY, GEZA GEORG, San Diego. Died November 1, 1977 in Cleveland, aged 75. Graduate of Orvosi Fakultasa Tudomanyegyetem, Budapest, 1926. Licensed in California in 1943. Dr. VonKomaromy was a retired member of the San Diego County Medical Society.

WHITELOCK, THOMAS SIDNEY, JR., San Digeo. Died December 2, 1977 in Tijuana, aged 73. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Dr. Whitelock was a retired member of the San Diego Medical Society.

WILSON, LELAND B., Ukiah. Died October 17, 1977 in Ukiah, aged 65, Graduate of the University of Nebraska College of Medicine, Omaha, 1952. Licensed in California in 1953. Dr. Wilson was a member of the Mendocino-Lake County Medical Society.

Proposed CMA Constitutional Amendments for Action in 1978

Fifteen Constitutional amendments were introduced in the 1977 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

* * *

Article I, Section 6.—Woman's Auxiliary to the California Medical Association

Introduced by: Frederick W. Ackerman, MD
Representing: Council
Author: Council

Constitutional Amendment 1-77
Committee G

RESOLVED: That Article I, Section 6.—Woman's Auxiliary to the California Medical Association be amended by deleting the words in brackets and adding the words in *italic* so that it now shall read:

Section 6.—[Woman's Auxiliary to the] California Medical Association *Auxiliary*

In addition to the organizational structure previously set forth in this Article, this Association may charter [a Woman's Auxiliary to] the California Medical Association *Auxiliary,* and components thereto, which shall be considered an integral part of the Association but which shall conduct its own organization and business separate and distinct from the Association and its Societies, subject to the following requirements:

(a) The name of the Auxiliary shall be ['Woman's Auxiliary to] the '*California Medical Association Auxiliary*' (hereinafter referred to as Auxiliary);

(b) The purpose of the Auxiliary shall be to promote the science and art of medicine, the protection of public health and the betterment of the medical profession, and to promote similar interests of its component Auxiliaries;

(c) The Auxiliary shall be composed of the component Auxiliaries and their members;

(d) Component Auxiliaries shall include all [women's] auxiliaries to Component Medical Societies of the California Medical Association heretofore or hereafter chartered by this Association; . . .

Article III.—Government of the Association, Part A—House of Delegates Section 1.—Composition

Introduced by: Frederick W. Ackerman, MD
Representing: Council
Author: Council

Constitutional Amendment 2-77
Committee G

RESOLVED: That Article III.—Government of the Association, Part A.—House of Delegates, Section 1.—Composition be amended by deleting the words in brackets so that it now shall read:

The House of Delegates shall consist of:

(a) Delegates elected by the members of component societies;

(b) Officers of the Association as hereinafter provided;

(c) Ex officio, with the right to vote, the Councilors;

(d) Ex officio, without the right to vote, [eighteen (18)] members of the Scientific Board selected as provided in the Bylaws;

(e) Ex officio, without the right to vote, the past presidents;

(f) Ex officio, without the right to vote, the officers, the delegates and alternate delegates to the American Medical Association, who are not otherwise members of the House of Delegates of this Association; and

(g) Delegates elected by duly enrolled medical students in good standing at accredited schools of medicine in California.

* * *

Article IV, Section 4, Funds, Property, Dues, Assessments and Expenditures

Introduced by: San Francisco Delegation
Author: Edward T. Kelley, MD

Constitutional Amendment 3-77
Committee F

RESOLVED: That Article IV, Section 4—Special Assessments, etc. of the Constitution of this Association be amended by inserting after the words "levied by"—a two-thirds vote of —so that Section 4 would read:

Section 4—Special Assessments, etc.

Funds may also be raised by any of the following methods: (a) publications of the Association; (b) voluntary contributions; (c) bequests, legacies, devises, and gifts; (d) special assessments levied by a *two-thirds vote of* the House of Delegates; and (e) in any other manner approved by the House of Delegates. In the event that the House of Delegates levies any special or other assessment than the annual assessment of dues, it may, in the resolution levying the assessment, fix and determine the time within which such assessment must be paid, the class or classes of members of the Association upon whom it is levied, and the penalty, if any, including forfeiture or suspension of membership in this Association or the component society, or both, to result from nonpayment thereof within the time prescribed.

Past President Voting Representation in the House of Delegates

Introduced by: Ralph C. Teall, MD
Representing: Past Presidents
Author: Ralph C. Teall, MD

Constitutional Amendment 4-77
Committee G

RESOLVED: That the CMA Past Presidents be accorded the privilege of voting in the CMA House of Delegates; and, be it further

RESOLVED: That Article III, Government of the Association, Part A, House of Delegates, Section 1, Composition, be amended by deleting the word in brackets and adding the word in *italic* so that it now shall read:

Section 1.—Composition

The House of Delegates shall consist of:

. . .

(e) Ex Officio, [without] *with* the right to vote, the past presidents.

* * *

Specialty Representation in the House of Delegates

Introduced by: F. Harold Johnson, MD
Author: F. Harold Johnson, MD

Constitutional Amendment 5-77
Committee G

RESOLVED: That Article III—Government of the Association, Part A.—House of Delegates, Section 1.—Composition,

be amended by adding a new subsection (d) and by renumbering the subsequent subsections.

(d) Delegates representing specialty sections or specialty organizations in those sections and elected by CMA members practicing within those specialties as provided in the Bylaws.

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Specialty Representation on the Council

Introduced by: F. Harold Johnson, MD
Author: F. Harold Johnson, MD

Constitutional Amendment 6-77
Committee G

RESOLVED: That Article III.—Government of the Association, Part B.—Council, Section 9—Composition, be amended by adding Subsection (f).

(f) Elected Councilors from specialty sections or mutually agreeable combinations of sections whose regular active CMA membership exceeds five thousand (5,000) and is approved by the CMA Council.

Specialty Representation on the Council—Election of Councilors

Introduced by: F. Harold Johnson, MD
Author: F. Harold Johnson, MD

Constitutional Amendment 7-77
Committee G

RESOLVED: That Article III—Government of the Association, Part B.—Council, Section 11.—Election of Councilors, be amended as follows by adding the words in *italic*.

District *and specialty section* councilors shall be elected in the manner and at the time specified in the Bylaws; provided, however, that at the first meeting of the House of Delegates after a district *and specialty section* councilor has been selected, his name shall be submitted to the House by the delegates from the district *or specialty section,* and (1) if there is no challenge by any delegate then the speaker shall declare his election completed, and (2) if any delegate shall challenge the election on any ground, including fitness of the nominee of the district *or specialty section* to serve as a district *or specialty section* councilor, the questions presented by the challenge shall be submitted to a Qualifications Committee consisting of the president, president-elect and one delegate, appointed by the speaker, from the councilor *or specialty section* district involved. The Qualifications Committee shall consider all grounds upon which the nominee is challenged and report back to the House. If the committee reports in favor of confirming the nominee's election, the speaker shall declare him elected. If the committee reports against confirming the nominee's election, a three-fourths affirmative vote shall be necessary to sustain the report of the committee, in which event the nominee shall be ineligible to serve as the district *or specialty section* councilor and the delegates from the district *or specialty section* shall immediately proceed with the selection of another nominee for the vacant office. If an adverse report of the Qualifications Committee is not sustained then the nominee shall be declared elected by the Speaker.

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Article III, Part B.—Council, Section 9.—Composition

Introduced by: Council
Representing: Committee of Specialty Societies
Author: Committee of Specialty Societies

Constitutional Amendment 8-77
Committee G

RESOLVED: That Article III, Part B, Section 9, of the Constitution of this Association be amended by adding a new subsection (f), which shall read:

(f) Councilors elected by the Specialty Delegation, as provided in the Bylaws.

Article III, Part A.—House of Delegates, Section 1.—Composition

Introduced by: Council
Representing: Committee of Specialty Societies
Author: Committee of Specialty Societies

Constitutional Amendment 9-77
Committee G

RESOLVED: That Article III, Part A, Section 1 of the Constitution of this Association be amended by deleting the words in brackets and adding the words in *italic* so that it now shall read:

Section 1.—Composition

The House of Delegates shall consist of:

(a) Delegates elected by the members of component societies;

(b) Delegates elected by members of specialty societies or organizations recognized by the House of Delegates, as provided in the Bylaws;

[(b)] *(c)* Officers of the Association as hereinafter provided;

[(c)] *(d)* Ex officio, with the right to vote, the councilors;

[(d)] *(e)* Ex officio, without the right to vote, eighteen (18) members of the Scientific Board selected as provided in the Bylaws;

[(e)] *(f)* Ex officio, without the right to vote, the past presidents;

[(f)] *(g)* Ex officio, without the right to vote, the officers, the delegates and alternate delegates to the American Medical Association, who are not otherwise members of the House of Delegates of this Association; and

[(g)] *(h)* Delegates elected by duly enrolled medical students in good standing at accredited schools of medicine in California.

* * *

Article III, Part A.—House of Delegates, Section 2.—Representation

Introduced by: Council
Representing: Committee of Specialty Societies
Author: Committee of Specialty Societies

Constitutional Amendment 10-77
Committee G

RESOLVED: That Article III, Part A, Section 2, of the Constitution of this Association be amended by adding the words in *italic,* so that it now shall read:

Section 2.—Representation

As the Bylaws shall provide, each component society shall be entitled to proportionate representation in the House of Delegates but with a minimum of two delegates. *As the Bylaws shall also provide, specialty societies or organizations recognized by the House of Delegates shall be entitled to representation.* As the Bylaws shall further provide, the duly enrolled medical students in good standing at each accredited school of medicine located in California shall be entitled to elect one delegate from each such school.

Article I, Section 5.—Component Society Chapters

Introduced by: Council
Representing: House Officer Component Unit
Author: Committee on Organizational Review and Planning (CORP)

Constitutional Amendment 11-77
Committee G

RESOLVED: That Article I, Section 5 of the Constitution of this Association be amended by deleting the words in brackets and adding the words in *italic* so that it now shall read:

Section 5.—Component Society Charters

Charters to component societies may be granted and revoked as hereinafter prescribed.

[One] *Two* charters may be issued to [a] component societ(y)*ies* that [is] *are* not limited as to geographical area or which overlap[s] the area covered by one or more existing component societies.

* * *

Article III, Part A, Section 7.—Issuance and Revocation of Charters

Introduced by: Council
Representing: House Officer Component Unit
Author: CORP

Constitutional Amendment 12-77
Committee G

RESOLVED: That Article III, Part A, Section 7 of the Constitution of this Association be amended by deleting the words in brackets and adding the words in *italics* so that it now shall read:

Section 7.—Issuance and Revocation of Charters

(a) The House of Delegates shall issue charters to medical societies of any county, any component society of at least 300 members which has exercised its option to become autonomous, [or] to any group of counties deemed eligible which have made proper application therefor, *and to any component society not limited as to geographical area authorized by the Bylaws.*

* * *

Article III, Part A, Section 4.—Terms of Delegates and Alternates

Introduced by: Council
Representing: House Officer Component Unit
Author: CORP

Constitutional Amendment 13-77
Committee G

RESOLVED: That Article III, Part A, Section 4 of the Constitution of this Association be amended by adding the words in *italic* so that it now shall read:

Section 4.—Terms of Delegates and Alternates

Delegates and alternates shall serve for two or three years as each component society may determine. One-half or one-third, as the case may be, of the allowed number shall be elected each year. Delegates and alternates elected from each school of medicine *and from the House Officer Component Society* shall serve for a term of one year.

Article III, Part B, Section 10.—Councilor Districts

Introduced by: Council
Representing: House Officer Component Unit
Author: CORP

Constitutional Amendment 14-77
Committee G

RESOLVED: That Article III, Part B, Section 10 of the Constitution of this Association be amended by deleting the words in brackets and adding the words in *italics,* so that it now shall read:

Section 10.—Councilor Districts

There are [12] *13* Districts as follows:

. . .

District Number Twelve, consisting of any society, *other than District 13,* which is not limited as to . . .

District Number Thirteen, consisting of the statewide House Officer Component Society, not limited as to geographical area; such society and its members shall not be considered to be members of any other Councilor District, and shall be entitled to elect one Councilor only when its membership exceeds 700 members, plus one additional Councilor for each additional 1,000 members.

* * *

Article III, Part B, Section 9.—Composition Student Representation on the Council

Introduced by: Ted Ganiats
Representing: Student Section—Liaison Committee to Medical Students
Author: Student Section—Liaison Committee to Medical Students

Constitutional Amendment 15-77
Committee G

RESOLVED: That Article III, Part B, Section 9 of the Constitution of this Association be amended by adding a new subsection (g), which shall read:

(g) The Chairman of the Student Section of the Liaison Committee to Medical Students, when he is a member of this Association, shall be an ex officio member of the Council, without the right to vote.

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When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

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GERIATRICIAN—Physician experienced in geriatrics and geriatric programs; to design and implement inpatient and outpatient geriatrics program; participate in approved internal medicine and surgery residency training programs; provide direct patient care. Send résumé to Russell D. Tyler, MD, Medical Director, Health Care Services, Santa Barbara General Hospital, P.O. Box 3650, Santa Barbara, CA 93105.

DELIGHTFUL COLORADO RURAL COMMUNITY seeks compatible medical group to render primary care in any or all specialties. Excellent recreational opportunities nearby. Contact, Administrator, Prowers Medical Center, Lamar, CO 81052.

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GASTROENTEROLOGIST (Clinical Hepatologist)—Major midwestern teaching and research medical center has a career opportunity for a Board Certified Gastroenterologist with expertise in clinical hepatology. Research opportunities will be available for a qualified candidate. The appointment affords the benefits of practicing as a member of a "closed staff" group practice with major facilities which include a 1,100-bed teaching hospital and 39 medical specialties located at our main campus and three suburban satellite clinics. Affiliation with major medical universities affords additional teaching opportunities. Salary and fringe benefits are competitive and the latter includes: malpractice insurance, generous vacation and travel time, a sound disability insurance, as well as life insurance, a tax sheltered annuity, a low cost lease car plan along with many other benefits. Interested physicians should forward their curriculum vitae in strict confidence. Reply Box No. 5962, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

THERAPEUTIC RADIOLOGIST—Major midwestern teaching and research medical center has an opportunity available for a Radiation Therapist in its Department of Therapeutic Radiology. The appointment affords the benefits of practicing as a member of a "closed staff" group practice with major facilities which include an 1,100-bed teaching hospital and 39 medical specialties located at our main campus and three suburban satellite clinics. Affiliation with major medical universities affords additonal teachng opportunities. The Department of Therapeutic Radiology is presently composed of three (3) staff physicians; three (3) residents in an approved Residency Program; eight (8) technologists, seven (7) of whom are registered in therapy; one (1) physicist; one (1) research assistant; one (1) nurse; and an 8-member clerical pool. Teaching involves other staff physicians, residents, 3rd and 4th year medical students, and radiation therapy technology students. Equipment includes a Clinac-12 Accelerator; 35 MEV Brown Boveri Betatron; stationary and rotational Cobalt; simulator and transverse tomography; afterloading interstitial and intracavitary; computer dosimetry; and mould room. The Department treats 900 new and recurrent cases every year. Excellent cooperation between the Therapeutic Radiology Department and other medical and surgical departments affords opportunities to treat patients with diversity of malignant diagnoses, in a multidisciplinary setting. We are in the position to offer an excellent individually based salary commensurate with experience, and a comprehensive benefit program. Interested physicians should forward their curriculum vitae in strict confidence. Reply Box 5963, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

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(Continued on Page 33)

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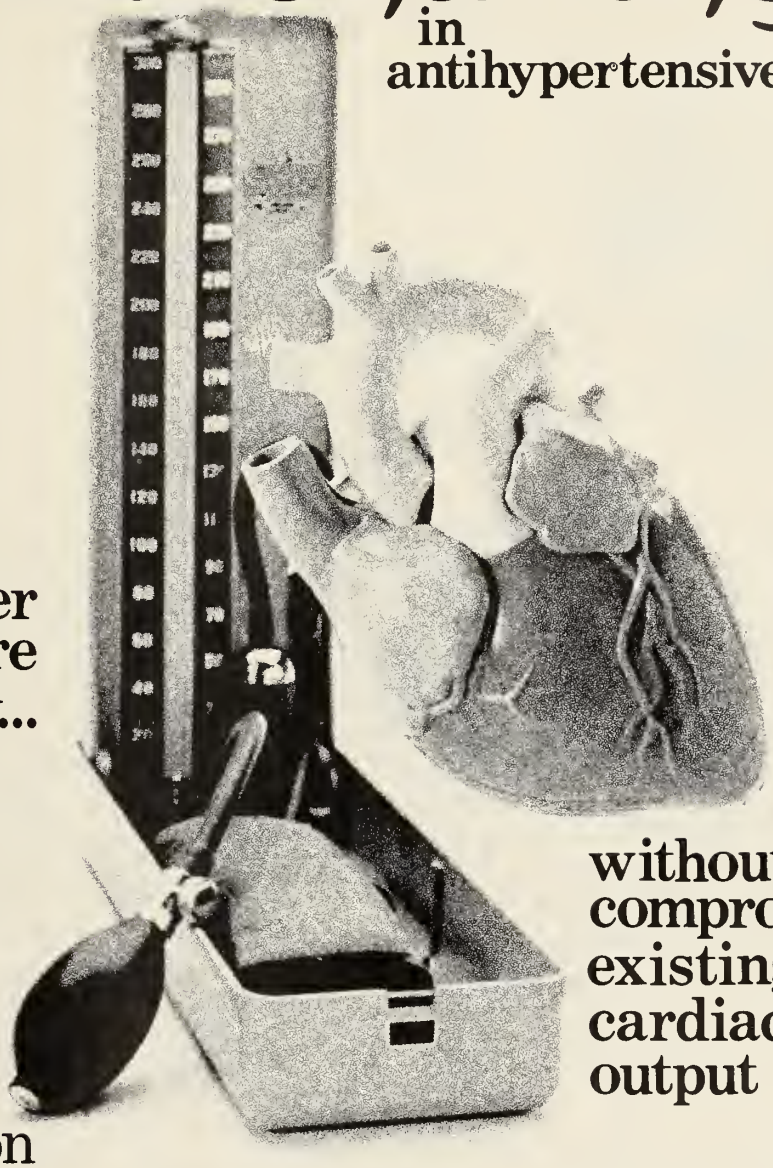

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It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

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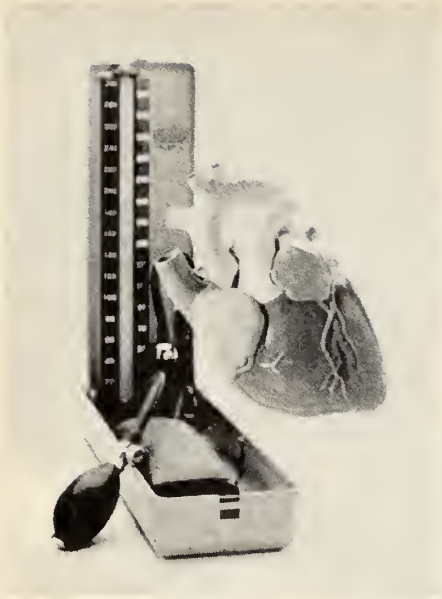

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Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

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(Continued from Page 30)

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GP needed for medical group. Complete x-ray and lab facilities. Starting salary is $4,000 per month, with increments to follow, until eventual partnership is reached. Free health and accident insurance, malpractice insurance, and medical association dues. Contact Mr. Fine, 2675 E. Slauson Ave., Huntington Park, CA 90255. Phone (213) 589-6681.

CALIFORNIA, BERKELEY - ALAMEDA COUNTY: Career-oriented emergency room physician wanted full-time, with contract group at active hospital. Over 30,000 visits yearly. Salary negotiable. Vacation and educational leave. New facility under construction. Board eligible emergency room preferred. Contact: Ralph Morris, MD, Herrick Memorial Hospital, 2001 Dwight Way, Berkeley, CA 94704.

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Knowledgeable P.A. with laboratory and x-ray capabilities in addition to clinical expertise. Single status assignment. (Must be bilingual in French-English.) One year contract. Excellent salary and fringe benefits; liberal R&R program with opportunity to travel. Responsible position for person who can work independently.

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PHYSICIANS

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ANESTHESIOLOGIST—Director of Education—Board Certified anesthesiologist with experience in residency training programs. A qualified individual will be given the responsibility to reinstate and direct a three year residency program in anesthesiology.

CARDIOLOGIST—Board Certified or Board Eligible—Seeking individual trained in Coronary Care, Noninvasive Cardiology and Rehabilitation Cardiology to participate in an active clinical research and teaching program.

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GASTROENTEROLOGIST—Board Certified gastroenterologist with special interest in gastrointestinal cancer.

GENERAL INTERNIST—Board Certified Internist for position in the Department of Medicine at central campus and a position for a Board Certified or Board Eligible General Internist at one of our suburban satellite clinics.

GENERAL SURGEON—Board Certified with 5-10 years experience, interested in either (1) general surgery, (2) intensive care, (3) head and neck, or (4) research as their area for concentration.

NEUROSURGEON—Board Certified or Board Eligible for a position in the Department of Neurological Surgery.

ORTHOPEDIC SURGEON—Board Certified or Board Eligible—The appointment would encompass activities at central campus and newly established suburban clinics. Position entails major surgery and participation in teaching at the central campus as well as outpatient practice and minor surgical procedures performed at the suburban clinics.

OTOLARYNGOLOGIST—Board Certified or Board Eligible. Appointment would encompass activities at our central campus and newly established suburban clinics. Position entails surgery and participation in teaching at the central campus as well as outpatient practice and minor surgical procedures performed at the suburban clinics.

PSYCHIATRIST—Board Certified or Board Eligible—Instructorships available with major universities, positions available at main campus as well as suburban centers. Areas of concentration for interested individuals should lie in either (1) clinical outpatient, (2) liaison consulting, (3) crisis intervention.

RADIOLOGIST—Board Certified. (1) General Diagnostic Radiologist. (2) Vascular Radiologist. The Department of Radiology performs all types of examinations, is active in Nuclear Medicine, Ultrasound and computed Tomography. The residency program is approved.

THERAPEUTIC RADIOLOGIST—Board Certified or Board Eligible Therapeutic Radiologist for position in the Department of Therapeutic Radiology.

Interested parties should send their curriculum vitae in strict confidence. Write BOX NO. 5949, WESTERN JOURNAL OF MEDICINE, 731 MARKET ST., SAN FRANCISCO, CA 94103.

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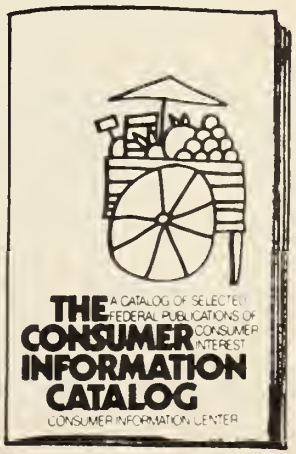

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CANCER

January 21—**Gastrointestinal Cancer.** SF Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. $15. Contact: Norma Schlager, SF Regional Cancer Foundation, 14th Ave. and Lake, San Francisco 94118. (415) 221-2132.

January 25—**Breakthroughs in Lymphomas and Leukemias.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: J. S. Bonorris, MD, Dir., Hematology Oncology, Hosp. of the Good Samaritan, 616 S. Witmer, Los Angeles 90017. (213) 488-8588.

January 27-28—**Cancer Update. A Clinical Approach to Diagnosis and Treatment of Common Malignancies—Breast, Colon, Lung and Prostate.** Peralta Hospital at Claremont Hotel, Berkeley. Friday-Saturday. Contact: Tish Hammerlee, Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 264.

January 30-31—**Cancer.** USC. Monday-Tuesday.

March 4—**What's New in Oncology 1978** (American Cancer Society at San Joaquin Delta College, Stockton. Saturday. 6 hrs. $20. Contact: Karen Schaefer, 1111 W. Robinhood Dr., Stockton 95207. (209) 477-2676.

March 9-12—**Modern Concepts in Oncology.** UCLA at Canyon Hotel, Palm Springs. Thursday-Sunday.

March 10-11—**Medical and Therapeutic Complications in Patients With Malignant Diseases.** Eisenhower Med. Center at Erawan Garden Hotel, Indian Wells. Friday-Saturday. 10 hrs. $50. Contact: John J. Deller, MD, Dir. of Education and Research, EMC, 39000 Bob Hope Dr., Palm Desert 92260.

March 10-12—**Cancer Endodurietherapy.** USC at Hotel Bonaventure, Los Angeles. Friday-Sunday. 22 hrs.

March 17—**Cancer of the Lung.** California Hospital Medical Center, Los Angeles. Friday. 5 hrs. $15. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 27-31—**Cancer.** STAN. Monday-Friday. 27 hrs. $265.

May 10—**Carcinoma of the Cervix: Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $25.

EMERGENCY MEDICINE

January 23-27—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Convention Center, San Diego. Monday-Friday. 40 hrs. $325.

January 23-27—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 30-February 3—**Emergency Medicine.** UCLA at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

February 26-March 3—**Emergency Medical Care Symposium II.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. $175.

March 20-24—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

April 3-7—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

April 15-22—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $300.

May 8-12—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

May 9-13—**Topics in Emergency Medicine.** UCSF at Ralph K. Davies Med. Center, San Francisco. Tuesday-Saturday.

May 10-12—**Emergency Room Radiology.** See Radiology, May 10-12.

MEDICINE

January 20-21—**New Developments in Stress Testing.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Miss Mary Ann McInerny, Dir., Extramural Programs Dept., Div. of Cont. Ed., ACC, 911 Old Georgetown Rd., Bethesda, MD 20014.

(Continued on Page 39)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

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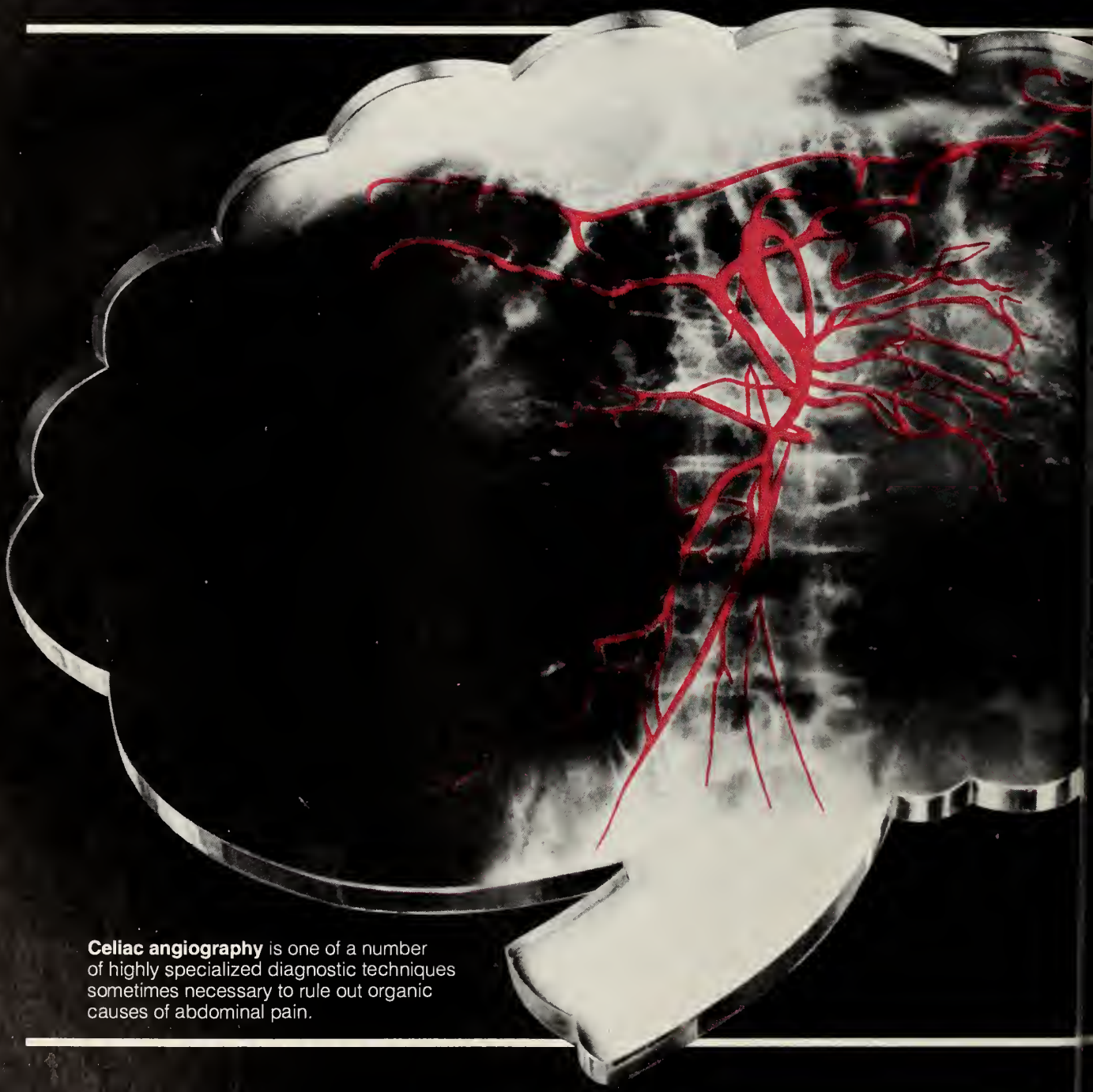

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Final classification of the less-than-effective indications requires further investigation.

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As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

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ROCHE

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(Continued from Page 35)

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** See Of Interest to All, January 21.

January 24-27—**Present Concepts in Internal Medicine.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 25—**Venous Thrombosis and Pulmonary Embolism—Dinner Meeting/Scientific Program.** LA Society of Internal Medicine at LA Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50. Contact: Thomas Yoshikawa, MD, LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

January 25-27—**Advances in Neurology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** UC Extension, Berkeley, and UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday. 12 hrs. $150. Contact: Medical Symposia, Div. of Letters and Sciences, UC Extension, Berkeley 94720. (415) 642-1061.

February 3-4—**Allergy.** STAN. Friday-Saturday. $80.

February 7-10—**Your Consultant Speaks—A Multidisciplinary Course for Dermatologists.** STAN at Lake Tahoe. Tuesday-Friday. 12 hrs. $225; $100 for residents and those in training.

February 8—**Cardiology-Nuclear Medicine Symposium.** See Radiology, February 8.

February 15-17—**Topics in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 22-24—**Daily Decisions in Lung Diseases.** Calif. Thoracic Society at Balboa Bay Club, Newport Beach. Wednesday-Friday. Contact: Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 23-25—**Advances in the Diagnosis and Therapy of Cardiovascular Disease—1978.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 3—**Diabetes Program—5th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday.

March 3-4—**Diagnosis and Management of Aphasia.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 12 hrs. $100.

March 6-9—**American College of Cardiology—27th Annual Scientific Session.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: Patrick Ziarnik, Dir., Annual Sci. Session Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 10-11—**Clinical Cardiology.** American College of Cardiology at Kauai Surf Hotel, Kauai, Hawaii. Friday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 16-19—**Viral Hepatitis.** UCSF at Hilton Hotel, San Francisco. Thursday-Sunday. 26 hrs. $145.

March 23-25—**Immunology and Allergy Conference—2nd Annual.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

March 28-31—**Consultant's Course in Dermatology—6th Annual.** UCSF. Tuesday-Friday. $250.

March 31-April 1—**Seminar on Thrombosis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 10 hrs. $75.

April 3-12—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 3-14—**Intensive Review of Internal Medicine.** USC. 12 days.

April 12-June 14—**Nephrology for the Practicing Internist.** UCLA. Wednesday evenings; 10 weeks.

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April 14-15—**Operative Arthroscopy.** See Surgery, April 14-15.

April 15-22—**Chronic Obstructive Pulmonary Disease—From the Beginning to the End.** International Center for Postgraduate Medical Education at Kona Surf Hotel, Hawaii. One week. 25 hrs. Contact: Ms. Kym Westenberg, ICPME, 3969 Cuervo, Santa Barbara 93110. (805) 967-0497.

April 19-21—**Echocardiographic Solutions to Clinical Cardiovascular Problems.** American College of Cardiology and UCLA at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 24-29—**American Academy of Neurology — Annual Meeting.** Bonaventure Hotel, Los Angeles. Monday-Saturday. $35, members; $55, nonmembers. Contact: Mr. Stanley A. Nelson, Exec. Dir., AAN, 4015 W. 65th St., Suite 302, Minneapolis, MN 55435. (612) 920-3636.

May 4-7—**American Society of Internal Medicine — Annual Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. Contact: ASIM, 535 Central Tower Bldg., 703 Market St., San Francisco 94103. (415) 777-1000.

May 13—**Controversies in Internal Medicine—2nd Annual.** San Jose Hosp. and Health Center, Inc., at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $35. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 16—**Common Skin Problems Seen in Office Practice.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, 199 E. Webster St., Colusa 95932. (916) 458-5844.

May 19—**American Heart Association, California Affiliate—Physicians' Scientific Sessions.** Vacation Village, San Diego. Friday. Contact: Marilyn Probst, AHA, Calif. Affiliate, 805 Burlway Rd., Burlingame 94010. (415) 342-5522.

May 22-26—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

OBSTETRICS AND GYNECOLOGY

January 19-21—**Pregnancy and Hypertension.** DREW at Hyatt House Hotel, Los Angeles. Thursday-Saturday. 20 hrs.

January 26-May 25—**Recent Advances in Obstetrics and Gynecology—2nd Annual.** UCLA. Thursday evenings. 32 hrs. $310.

January 28-30—**Comprehensive Laparoscopy.** UCSD at Kona Kai Club, San Diego. Saturday-Monday. 16 hrs. $375.

February 11-12—**Obstetrical and Gynecological Forum.** LA Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Ms. Dee Davis, Exec. Sec., LA Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 15-19—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Of Interest To All, February 15-19.

March 9-10—**Gynecological Urology Seminar.** See Surgery, March 9-10.

April 10-12—**Antenatal Assessment of the Fetus From Conception to Delivery.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 21 hrs. $150.

May 6-8—**Comprehensive Laparoscopy: Current Principles and Practice.** UCSD at Hotel del Coronado, Coronado. Saturday-Monday. 16 hrs. $375.

PEDIATRICS

January 19—**Parmelee Memorial Lecture—17th Annual.** American Academy of Pediatrics, Calif. Chap. 2; and LA Pediatric Society at Hilton Hotel, Los Angeles. Thursday. Contact: LA Pediatric Society, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

January 26-28—**Troubled Youth.** See Psychiatry, January 26-28.

January 26-29—**Winter Ski and Study Symposium—3rd Annual.** American Academy of Pediatrics, District IX, Chapter 2, at Mammoth Mountain. Thursday-Sunday. $135, members; $160, non-members. Contact: Calif. Chapter 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

January 27-29—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 27-29.

January 28-29—**Pediatrics for the Primary Physician: A Practical Update.** See Of Interest To All, January 28-29.

February 10—**Pediatric Otolaryngology.** See Surgery and Anesthesiology, February 10.

February 10-11—**Diagnosis and Management of the MBD Syndrome.** See Psychiatry, February 10-11.

February 15—**Pediatric Hematology.** LLU. Wednesday. 8 hrs. Contact: Sanford Schneider, MD, A531, LLU Med. Ctr., Loma Linda 92354. (714) 796-7311, ext. 2832.

February 23-25—**Development in Infancy and Childhood—Annual Winter Meeting.** Children's Hospital Med. Ctr., Oakland, at Sahara Tahoe Hotel, So. Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, CHMC, 51st and Grove Sts., Oakland 94609.

February 24-26—**Recent Advances in Patterns of Infant Development: Relevance for Later Life.** So. Calif. Soc. for Child Psychiatry; Com. on Psychiatric Dimensions of Infancy, AACP; Chap. 2, ACP, at South Coast Plaza Hotel, Costa Mesa. Friday-Sunday. 18 hrs. Contact: SCSCP, 14724 Ventura Blvd., No. 604, Sherman Oaks 91403. (213) 986-8066.

March 17-19—**Combined Southern California Pediatric Postgraduate Meeting—8th Annual.** American Academy of Pediatrics, District IX, Chapter 2, at Riviera Hotel, Palm Springs. Friday-Sunday. $135, members; $150, non-members. Contact: Calif. Chapter 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 5-7—**General Pediatrics.** American Academy of Pediatrics at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 7-8—**Common Problems in Ambulatory Pediatrics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 8-13—**American Academy of Pediatrics—Spring Session.** Century Plaza Hotel, Los Angeles. Saturday-Thursday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

May 1-5—**Pediatric Review.** USC. Monday-Friday.

May 11-13—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 13-20—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 28 hrs. $300.

May 20-21—**Neuropediatrics.** UCLA. Saturday-Sunday. 11 hrs. $165.

May 27-29—**American Academy of Pediatrics, California Chapter I, District IX.** Hyatt House, Monterey. Saturday-Monday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

PSYCHIATRY

January 20-22—**Psychoanalytically Oriented Psychotherapy: A Retrospective.** UCSF. Friday-Sunday. 12 hrs. $45.

January 26-28—**Troubled Youth.** USC at Vacation Village, San Diego. Thursday-Saturday.

January 27-28—**Practical Psychiatry.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 12 hrs. $125.

January 29-February 3—**Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 8—**Overview of Newer Approaches for Troubled Patients.** LLU. Wednesday. 4 hrs. $25.

February 10-11—**Diagnosis and Management of the MBD Syndrome.** American Academy of Child Psychiatry at Red Lion Motor Inn, Sacramento. Friday-Saturday. $20. Contact: Gordon D. Jensen, MD, Dept. of Psychiatry, UCD, Davis 95616.

April 15-16—**Stress: Psychological Management.** UCLA at Santa Cruz. Saturday-Sunday.

May 19-21—**Treatment of Schizophrenia.** UCSF. Friday-Sunday.

RADIOLOGY AND PATHOLOGY

January 16-20—**Computed Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $295.

January 17—**Updating Radiation Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

January 27-29—**Los Angeles Radiological Society—30th Annual Mid-Winter Meeting.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** See Medicine, January 27-29.

February 8—**Cardiology-Nuclear Medicine Symposium.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 6 hrs. $45. Contact: Leonard Swanson, MD, Dir., Nuc. Med., Hosp. of the Good Samaritan, 616 S. Witmer, Los Angeles. (213) 488-8123.

February 19-24—**Interpretative Enzymology.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Friday. 25 hrs.

February 21—**Clinical Laboratory Tests: Results, Clinical Application and New Laboratory Tests.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 1—**Computerized Tomography—Dinner Meeting/Scientific Program.** LA Soc. of Internal Medicine at LA Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50. Contact: Thomas Yoshikawa, MD, LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

March 4-5—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 9 hrs. $100.

March 5-10—**Medical Imaging in the High Sierra.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Sahara Tahoe Hotel, Lake Tahoe. Sunday-Friday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

March 6-10—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $275.

March 11-12—**A Practical Course in B-Scan Ultrasound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 9 hrs. $125.

April 9-14—**American College of Radiology—Annual Meeting and Categorical Course.** Town and Country Hotel, San Diego. Sunday-Friday. Contact: Ms. Sheila Aubin, Meeting Manager, ACR, 20 N. Wacker Dr., Chicago, IL 60606. (312) 236-4963.

May 10-12—**Emergency Room Radiology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

May 12—**Radiology Symposium.** UCD at Red Lion Motor Inn, Sacramento. Friday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY AND ANESTHESIOLOGY

January 16-20—**Otologic Surgery—13th Annual Course.** Ear Research Institute, Los Angeles. Monday-Friday. 45 hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 20-21—**Hand Injuries and Infections.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 9 hrs. $150.

January 21—**Ophthalmic Plastic Surgery.** Jules Stein Eye Institute and UCLA. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

January 22-26—**Ophthalmology and Otolaryngology—47th Annual Mid-Winter Clinical Convention.** The Research Study Club of Los Angeles, Inc., at Hilton Hotel, Los Angeles. Sunday-Thursday. 28 hrs. $175. Contact: Mr. Richard Pruter, Exec. Sec., P. O. Box 49412, Los Angeles 90049. (213) 879-0143.

January 27-29—**Pediatric Anesthesiology—16th Clinical Conference.** Children's Hospital of Los Angeles at Hilton Hotel, Los Angeles. Friday-Sunday. 15 hrs. $135. Contact: Wayne Herbert, MD, Children's Hosp., 4650 Sunset Blvd., Los Angeles 90027. (213) 660-2450, ext. 2262.

February 3-4—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute and UCLA. Friday-Saturday. $300. Contact: Lu Hendricks, Academic Prog. Admin., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

February 3-4—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

February 5-8—**Surgical Anatomy—19th Annual Theodor Billroth Course.** LLU. Sunday-Wednesday. 32 hrs. $200.

February 10—**Pediatric Otolaryngology.** USC. Friday.

February 10-11—**Ophthalmology Symposium.** So. Calif. Permanente Med. Group at Little America Westgate Hotel, San Diego. Friday-Saturday. Contact: Shirley Gach, SCPMG, 4900 Sunset Blvd., Room 6014, Los Angeles 90027. (213) 667-4241.

Stanford University School of Medicine

Office of Postgraduate Medical Education

announces a multidisciplinary course on

CANCER

MARCH 27-31, 1978

at Stanford University

A five-day multidisciplinary symposium on "Cancer" will be presented for physicians and surgeons who deal with problems related to neoplastic disorders. Lectures, case presentations, and informal seminars will provide each registrant with an opportunity to assess his present knowledge and practice and to acquire new information and skills of clinical pertinence. General lectures will cover:

- Molecular Biology of Cancer
- Carcinogenesis
- Cell Cycles and Cytokinetics
- Ultrasound
- Scintigraphy
- Body Scanning—Computerized Axial Tomography
- Staging
- Principles of Radiation Therapy
- Principles of Chemotherapy
- Specific Chemotherapeutic Agents
- Adjuvant Chemotherapy
- Endocrine Therapy and Ablative Procedures
- Tumor Immunology
- Management of Infection
- Use of Blood Components
- Hodgkins and the Other Lymphomas
  - Diagnosis and Classification
  - Staging Procedures
  - Radiation Therapy and Chemotherapy
- Breast
  - Diagnosis and Staging
  - Surgery and Radiation Therapy
  - Medical Management
- Skin Cancer
- Ovarian and Uterine Cancer
- Bronchogenic Carcinoma—Medical Management

Concurrent elective afternoon sessions will include:

- Hematology: AML, ALL, CML, CLL, and Plasma Cell Neoplasms
- Head and Neck: Primary Sites—Surgery, Radiotherapy, and Chemotherapy; Thyroid

Faculty for the course will consist of 30 members of the Stanford University Faculty.

The Postgraduate Medical Education Program of Stanford University School of Medicine is fully accredited by the AMA and CMA continuing education programs, with this course being acceptable for up to 26½ hours of Category I credit. Application has been made for approval by the American Academy of Family Physicians.

Tuition: $265. Registration is required no later than Mar. 24.

For registration, brochure, or further information address:

Office of Postgraduate Medical Education
Room TA-145
Stanford University Medical Center
Stanford, California 94305
Phone (415) 497-5594

February 28-March 3—**Diagnosis and Management of Acoustic Neuromas and Skull Base Tumors.** Ear Research Institute, Los Angeles. Tuesday-Friday. 32 hrs. $400. Contact: William F. House, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 3-4—**Development and Management of Aphasia.** See Medicine, March 3-4.

March 6-17—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Fred H. Linthicum, MD, Dir. of Education, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

March 8—**General Surgery Seminar.** LLU. Wednesday. 4 hrs. $25.

March 9-10—**The Orbit: Diagnostic Approaches and Management Decisions.** PMC at Stanford Court Hotel, San Francisco. Thursday-Friday. $225.

March 9-10—**Gynecological Urology Seminar.** American Urological Association at Airport Marina Hotel, Los Angeles. Thursday-Friday. 16 hrs. $180. Contact: Gynecological Urology Seminar, c/o Joseph J. Kaufman, MD, UCLA Med. Ctr., Div. of Urology, Los Angeles 90024.

March 11—**Cataract Surgery and Intraocular Lens.** Jules Stein Eye Institute and UCLA. Saturday. 8 hrs. $225. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

March 12-17—**Anesthesiology 1978—4th Annual Winter Meeting.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Mammoth Lakes. Sunday-Friday. 20 hrs. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

March 19-23—**International Anesthesia Research Society—52nd Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: B. B. Sankey, MD, Exec. Sec., IARS, 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

March 21—**Urology—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 29-April 2—**Controversial Areas in Surgery—15th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday. 13 hrs. $195.

March 30-31—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs.

April 2-6—**Vascular Surgery—6th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Sunday-Thursday.

April 7-8—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

April 12-14—**Maxillofacial Trauma—Soft Tissues Reconstruction and Facial Nerve Injury.** UCSF. Wednesday-Friday.

April 13-15—**General Surgery—Annual Course.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 14-15—**Operative Arthroscopy.** UCLA. Friday-Saturday. 12 hrs. $315.

April 15-22—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 16-21—**California Society of Anesthesiologists — 2nd Hawaii Seminar.** Hyatt Regency Hotel, Waikiki-Honolulu. Sunday-Friday. 20 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

April 18—**Orthopaedics—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

April 20-21—**Current Concepts of Macular Structure, Function and Disease—9th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute and UCLA at Century Plaza Hotel, Los Angeles. Thursday-Friday. $225. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

April 20-21—**Current Problems in Intensive Care: The Cardiac Surgical Patient.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 11 hrs. $125.

April 29-May 6—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $275.

May 1-12—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Fred H. Linthicum, MD, Dir. of Education, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

May 6—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 6-7—**American Society of Anesthesiologists Workshop.** St. Francis Hotel, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

May 11-12—**Office Orthopedics.** USC. Thursday-Friday.

May 18-20—**Neurosurgery.** UCSF at Sheraton Palace, San Francisco. Thursday-Saturday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

January 18-20—**Infectious Disease.** USC. Wednesday-Friday.

January 19-20—**Biofeedback Techniques in Physical Medicine and Rehabilitation.** Herrick Memorial Hospital, Berkeley. Thursday-Friday. Contact: Marie Ham, Med. Staff Sec., Herrick Mem. Hosp., 2001 Dwight Way, Berkeley 94704. (415) 845-0130, ext. 418.

January 19-20—**Longevity Research Institute—2nd Annual Meeting.** With LLU at Longevity Research Institute, Santa Barbara. Thursday-Friday. 10 hrs. Contact: Mr. Bob Palmer, LRI, 1121 E. Cabrillo Blvd., Santa Barbara 93103. (805) 966-3967.

January 19-21—**Medical Aspects of Aging.** UCLA at Sheraton Universal Hotel, Universal City. Thursday-Saturday.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** Continuing Medical Education/San Luis Obispo Consortium at Hilton Inn, San Luis Obispo. Saturday. 5 hrs. $25 for non-consortium members. Contact: Billy Mounts, MD. Chr., CME/SLO Consortium, P.O. Box 319. San Luis Obispo 93406.

January 23-27—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 27 hrs. $265.

January 28-29—**Pediatrics for the Primary Physician: A Practical Update.** UCLA. Saturday-Sunday. 10 hrs. $135.

January 28-29—**Holistic Health IX: Nutrition: Science, Art and Culture.** East West Academy of Healing Arts; UC, Berkeley, Dept. of Nutritional Sciences; Health Training Ctr., Calif. State Dept. of Health. in Los Angeles. Saturday-Sunday. 9 hrs. $70, EWAHA members; $75, non-members. Contact: EWAHA, PO Box 31211, San Francisco 94131. (415) 285-9400.

January 30-February 4—**Family Practice Refresher Course—9th Annual.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 2-3—**Family Planning, Human Sexuality and Venereal Disease.** DREW at Hyatt House, Long Beach. Thursday-Friday. 15 hrs.

February 3-5—**American Medical Association—Regional Program.** Sahara Tahoe Hotel, Stateline. Friday-Sunday. Contact: UCD or Mr. G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

February 8-11—**Primary Care—Current Management of Common Office Problems.** UCSF at Golden Gate Holiday Inn, San Francisco. Wednesday-Saturday.

February 10-11—**Alcoholism Update—4th National Seminar.** Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 10-12—**Headaches: Evaluation and Management.** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. 18 hrs.

February 10-12—**Health Aspects of Human Sexuality.** Human Sexuality Program, UCSF. Friday-Sunday. Contact: John Holland, Human Sexuality Program, UCSF, 350 Parnassus Ave., Suite 700, San Francisco 94143. (415) 666-4787.

February 12-13—**Workshop on Alcoholism—A Clinical Approach for Health Professionals.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Monday. 13 hrs.

February 13-17—**LLU Alumni Association—Annual Postgraduate Convention.** LLU. Monday-Friday.

February 15-17—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hospital and Med. Ctr., P. O. Box 7921, San Francisco 94120. (415) 567-6600, ext 2401.

February 15-19—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** Tyler Med. Clinic and Century City Hosp. at Hilton Hotel, Las Vegas. Wednesday-Sunday. Contact: Jaroslav J. Marik, MD, 921 Westwood Blvd., Los Angeles 90024.

February 16-17—**Selected Topics in Geriatric Medicine.** STAN and Palo Alto VA Hospital at Stanford. Thursday-Friday.

February 19-24—**Caring for Older Persons.** Medical Communications and Services Assn. at Kona Surf Hotel, Kailua, Kona, Hawaii. Sunday-Friday. 31 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

February 22-24—**Daily Decisions in Lung Diseases.** Calif. Thoracic Society at Balboa Bay Club, Newport Beach. Wednesday-Friday. $150, members; $175, nonmembers. Contact: Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 25-26—**National Symposium on Aging.** UCSF. Saturday-Sunday.

February 26-March 3—**Clinical Management of Sexual Problems.** Medical Communications and Services Assn. at Sheraton Hotel, Molokai, Hawaii. Sunday-Friday. 30 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

February 27-March 3—**Basic Science for Clinicians.** STAN. Monday-Friday. 25½ hrs. $265.

March 3-4—**Diagnosis and Management of Aphasia.** See Medicine, March 3-4.

March 4—**Controversies in Applied Immunotherapy.** UCSF at Children's Hospital, San Francisco. Saturday.

March 4-5—**Current Trends in the Management of Common Genetic Disorders.** UCLA. Saturday-Sunday.

March 6-8—**Diagnosis, Treatment and Prevention of Genetic Disease.** American College of Physicians; Harbor Gen. Hospital; Nat'l Foundation-March of Dimes at Riviera Hotel, Palm Springs. Monday-Wednesday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia 19104.

ALLERGY

A Postgraduate Medical Education Course

STANFORD UNIVERSITY
SCHOOL OF MEDICINE
DIVISION OF IMMUNOLOGY

February 3 and 4, 1978

The program is designed for nonallergists who care for patients with allergic problems–pediatricians, general and family practitioners, internists, ear, nose and throat specialists, dermatologists, and emergency room physicians–and should provide the practicing physician with a rational approach to the diagnosis and management of allergic disorders.

Tuition—$80; advance registration is requested.

Course is fully accredited by AMA and CMA for 9 hours Category I; AAFP approval requested.

For registration, brochure, or information:
Office of Postgraduate Medical Education, Room TA-145
Stanford University School of Medicine
Stanford, California 94305 Telephone: (415) 497-5594

March 7-May 23—**Bedside Clinics.** USC at Children's Hospital, Los Angeles. Tuesday evenings.

March 8-10—**Neurology for Non-Neurologists.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday. 22 hrs.

March 10-12—**American Medical Association—Regional Seminar.** Newporter Inn, Newport Beach. Friday-Sunday. Contact: G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

March 11-12—**Liaison Psychiatry.** UCLA. Saturday-Sunday. 14 hrs.

March 14-18—**Sports Medicine for the Primary Physician.** Univ. of Hawaii School of Medicine at Princess Kaiulani Hotel, Honolulu. Tuesday-Saturday, 18 hrs. $200. Contact: Univ. of HI Sports Medicine Course, Hawaii Conference Services, P.O. Box 22670, Honolulu 96822.

March 15-18—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Wednesday-Saturday.

March 17-19—**Family Practice—Intensive Review.** DREW. Friday-Sunday.

March 17-22—**California Medical Association—107th Annual Session.** Fairmont Hotel, San Francisco. Friday-Wednesday. Contact: Linda Ramsey, CMA.

March 25—**Burn Care for the Non-Burn Physician.** Alta Bates Hospital, Berkeley. Saturday. Contact: Dept. of Medical Education, Alta Bates Hosp., 1 Colby Plaza, Berkeley 94705. (415) 845-7110, ext. 2055.

April 2-7—**Electrophysiology.** USC at Erawan Gardens, Palm Springs. Sunday-Friday.

April 8-9—**Stress: Medical Management.** UCLA at Palm Springs. Saturday-Sunday. 14 hrs.

April 12—**The Prostate.** LLU. Wednesday. 4 hrs. $25.

April 17-19—**Stress Workshop.** UCLA at Yosemite. Monday-Wednesday. 15 hrs.

April 22-23—**Practical Dermatology for the Primary Care Physician.** UCLA. Saturday-Sunday.

April 22-29—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 27-29—**San Joaquin Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Richard Manley, CMA.

April 29-30—**Sports Medicine.** UCLA. Saturday-Sunday.

May 15-21—**Diving Medicine.** UCSF at VA Hospital, Fresno. One week.

May 19-21—**Health Aspects of Human Sexuality.** Human Sexuality Program, UCSF. Friday-Sunday. Contact: John Holland, Human Sexuality Prog., UCSF, 350 Parnassus Ave., Suite 700, San Francisco 94143. (415) 666-4787.

(Continued on Page 46)

COLBY PROCLAIMS WOMAN SUFFRAGE

Signs Certificate of Ratification at His Home Without Women Witnesses.

MILITANTS VEXED AT PRIVACY.

Wanted Movies of Ceremony, But Both Factions Are

WASHINGTON, Aug. 26, 1920—

Social Security Bill Is Signed; Gives Pensions to Aged, Job

Roosevelt Approves Message Intended to Benefit 30,00 Persons When States Adopt Cooperating Laws-He C the Measure 'Cornerstone' of His Economic Progra

WASHINGTON, Aug. 14 The Social Security Bill, pr a broad program of unempl insurance and old age p and counted upon to bene 20,000,000 persons, became day when it was signed b dent Roosevelt in the pres those chiefly responsible f ting it through Congress.

Mr. Roosevelt call the "the cornerstone in a which is being m s comple ri to

SENATE APPROVES 18-YEAR OLD VOTE IN ALL ELECTIONS

Amendment to Constitution is Sent to House, Where Passage is Expected

WASHINGTON, March 10, 1971—The Senate approved today, 94 to 0, and sen

TRUMAN CLOSES ITED NATIONS CONFEREN WITH PLEA TO TRANSLATE CHARTER INTO DEEDS

NEW WORLD HOPE

President Hails 'Great Instrument of Peace,' Insists It Be Used

HISTORIC LANDMARK

Meeting Gives Standing Ovation as Executive Pictures Peace Gain

"If we fail to use it," he declared to the solemn final meeting of the delegates, 'we shall betray all of those who have died in order that we might meet here in freedom and safety to create it.'

"If we seek to use it selfishly—for the advantage of any one nation or any small group of nations—we shall be equally guilty of that betrayal."

Fervent Interpolation

The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session the President accompanied the

SIGNI

the Draf Ends No

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Army that

PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

PMA
THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION
1155 FIFTEENTH ST., N. W. WASHINGTON, D. C. 20005

(Continued from Page 43)

May 21-26—**Orthopaedic Symposium for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday.

Audio-Digest Foundation. A nonprofit educational subsidiary of the California Medical Association. Twice-a-month tape-recorded summaries of leading national meetings. Services by subscription in: Anesthesiology, Family Practice, Internal Medicine, Obstetrics/Gynecology, Ophthalmology, Otorhinolaryngology, Pediatrics, Psychiatry, Surgery. ($90.00 per year for 24 one-hour cassettes or reels.) New catalog of lectures and panel discussions in all areas of medical practice also available, as well as cassette album condensations of the following 1977 specialty meetings: postgraduate courses from the annual meeting of the American Psychiatric Assn., workshops from the annual meeting of the American College of Physicians, and postgraduate courses from the annual sessions of the American College of Obstetricians and Gynecologists. For further information on subscriptions, catalogs and special courses, contact Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

February 13-17—**Ninth Annual Family Practice Review.** Sheraton Portland Hotel, Lloyd Center, Portland. Contact: J. S. Reinschmidt, MD, Department of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

January 18—**Circuit Course on Stroke Prevention.** Salem Memorial Hospital, Salem. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 25—**Circuit Course on Stroke Prevention.** Rogue Valley Memorial Hospital, Medford. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 26—**Circuit Course on Stroke Prevention.** Sacred Heart Hospital, Eugene. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

February 1—**Circuit Course Program on Endocrinology.** Columbia Memorial Hospital, Astoria. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

February 8—**Circuit Course Program on Advances in Pediatrics.** Presbyterian Inter-Community Hospital, Klamath Falls. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

February 9—**Circuit Course Program on Advances in Pediatrics.** St. Charles Medical Center, Bend. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

March 2—**Circuit Course Program on Advances in Pediatrics.** St. Anthony Hospital, Pendleton. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

March 2—**Circuit Course on Disorders of the Lower GI Tract.** Albany General Hospital, Albany. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

March 2—**Circuit Course Program on Evaluation of the Severely Injured.** Josephine General Hospital, Grants Pass. Contact Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

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In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

January 18-20—**Problems in Clinical Endocrinology—American College of Physicians.** Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Contact: American College of Physicians, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

January 23-24—**Coronary Artery Surgery—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Jan. 23, Wenatchee. Contact: William M. McKee, MD, P. O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Jan. 24, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

January 25-27—**Coronary Artery Disease—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Jan. 25, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Jan. 26, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Jan. 27, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

January 26-28—**The Macula and Fluorescein Angiography—Washington State Academy of Ophthalmology President's Meeting.** Thursday-Saturday. Washington Plaza Hotel, Seattle. 15 hrs. Contact: Charles E. Boylan, MD, 1601 16th Ave., Seattle, WA 98122. (206) 325-8500.

February 3-4—**Pharmacology for the Practitioner.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle WA 98101. (206) 223-6898.

February 13-16—**Pediatric Gynecology—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Monday, Feb. 13, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Tuesday-Wednesday, Feb. 14-15, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, Feb. 15-16, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 14-17—**Oncology.** Tuesday-Friday. 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. Contact: College of Medical Education, University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

February 15—**Headaches—Univ. of Wash. General Medicine Sessions in Anacortes, Washington.** Contact: Harry Eiesland, MD, 24th and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

February 17-18—**Controversies in Obstetrics and Gynecology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

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February 23-24—**Lower Intestinal Diseases—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Feb. 23, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Feb. 24, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

March 3-4—**Hypertension Symposium.** Friday-Saturday. Big Sky, Montana. Contact: D. Frank Johnson, MD, Dir. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 3-4—**Nephrology.** Friday-Saturday. Glasier Auditorium, Swedish Hospital and Medical Center, Seattle. Contact: Dept. of Med., Ed., Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2266.

March 6-10—**The Medical Model of the Future: Holistic Health.** Monday-Friday. Sun Valley, Idaho. 20 hrs. Fee: Physicians, $275; others, $225. Contact: Paulette Gregg, Box 992, Sun Valley, ID 83353. (208) 726-4248.

March 12-16—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Sunday-Monday, March 12-13, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. Tuesday-Wednesday, March 14-15, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, March 15-16, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 16-17—**Internal Medicine.** Thursday-Friday. Tacoma, Wash. Contact: Mrs. Maxine Bailey, College of Medical Education, University of Puget Sound, 1500 N Warner, Tacoma, WA 98416. (206) 756-3152.

March 17-18—**Surgery of the Liver and Biliary Tract.** Friday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

March 22-24—**Antibiotics and Infectious Disease—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, March 22, Great Falls. Contact: Mr. John Breeden, PO Box 2829 Great Falls, MT 59403. (406) 453-1493. Thursday, March 23, Billings. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, March 24, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

March 24-25—**Gynecologic Cancer.** Friday-Saturday. Glasier Auditorium, Swedish Hospital and Medical Center. Contact: Dept. of Med. Ed., Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2266.

March 27-28—**Premature Coronary Artery Disease and Lipoprotein—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, March 27, Wenatchee. Contact: William M. McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, March 28, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

March 30-31, April 6-7—**Endocrine Glands.** Thursdays-Fridays. 8 am-10 am, Good Samaritan Hospital, Puyallup, Wash. Contact: Mrs. Maxine Bailey, College of Medical Education, University of Puget Sound, 1500 N Warner, Tacoma, WA 98416. (206) 756-3152.

Index to The Western Journal of Medicine Advertising

Beth Israel Hospital
1978 Winter Conference Schedule 2

Boehringer Ingelheim Ltd.
Catapres 6, 7, 8

Burroughs Wellcome Co.
Neosporin Topical 29

Classified 30, 33, 34

Dorsey Laboratories
Recommendables 18, 19

Eli Lilly and Company
Kefzol I.M./I.V. 9

Endo Inc.
Percocet 5 ..... 20, 21

Geigy Pharmaceuticals
Brethine 23, 24

International Center for Postgraduate Medical Education
Chronic Obstructive Pulmonary Disease 20

Longevity Research Institute
2nd Annual Education Conference 16

Mead Johnson Laboratories
Colace 25
Vasodilan 26, 27
Quibron 28

Medical World News 3

Merck Sharp & Dohme
HydroDIURIL 12, 13
Aldomet 31, 32

New Orleans 41st Annual Medical Assembly 2

Pharmaceutical Manufacturers Association 44, 45

Roche Laboratories
Gantanol ..... 2nd Cover, 1, 2
Librax 36, 37, 38
Valium ..... 3rd and 4th Covers

Smith Kline & French Co.
Dyazide 17

Somatics Conference Associates
Explorers of Humankind 15

South Bay Hospital Annual Medical Symposium
Critical Care—1978 22

Stanford University Medical Center
Multidisciplinary course—CANCER 41
Postgraduate Medical Education Course—ALLERGY 43

U.S. Army Medical Recruiting 47

USC School of Medicine
26th Annual Intensive Review of Internal Medicine 39

Warren-Teed Pharmaceutical Inc.
Kaon Elixir - Kaon Tabs 10, 11

Westwood Pharmaceuticals Inc.
PreSun 5

THE WESTERN Journal of Medicine

VOLUME 128 • NUMBER 2 **FEBRUARY 1978**

101 *Ampicillin-Resistant Hemophilus influenzae—Emergence in California's Central Valley*
DAN M. GRANOFF, MD; MILLIE BASDEN, RN, and RICHARD ROCKWELL, MA

106 *Treatment of Malignant Pheochromocytoma* HENRY DRASIN, MD

112 *Head Injury and Early Signs of Tentorial Herniation—A Management Dilemma*
JULIAN T. HOFF, MD; ROBERT SPETZLER, MD, and DAVID WINESTOCK, MD

MEDICAL PROGRESS
117 *Viral Hepatitis* GARY L. GITNICK, MD

SPECIALTY CONFERENCE
127 *Differential Diagnosis of Congenital Heart Disease in the Newborn*
Participants: STANLEY E. KIRKPATRICK, MD; ADALINE CORRIN, MD; CHARLES HIGGINS, MD, and WILLIAM L. NYHAN, MD, PhD
Departments of Pediatrics and Radiology, University of California, San Diego, School of Medicine, and University Hospital, San Diego

MEDICAL STAFF CONFERENCE
133 *Hemochromatosis* Chief Discussant: LLOYD H. SMITH, JR., MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE
142 *Anesthesiology—Epitomes of Progress*

EDITORIALS
151 • *Avicenna Revisited* • *Trends in the Science and the Art* • *Progress With Hepatitis B Virus—Editorial Review* • *Newborn Infants With Congenital Heart Disease*

CASE REPORTS
159 *Human Rabies*
LARRY J. BARAFF, MD; BARRY HAFKIN, MD; PAUL F. WEHRLE, MD; RICHARD W. EMMONS, MD; ROBERT A. GUNN, MD; GARY D. OVERTURF, MD, and EVAN STEINBERG, MD

165 *Acute Suppurative Thyroiditis—Diagnostic, Metabolic and Therapeutic Observations*
MARTIN E. ADLER, MD; GEORGE JORDAN, MD, and ROBERT M. WALTER, JR., MD

CORRESPONDENCE
169 • *Mesothelioma in Shipyard Workers* • *Information Systems for Small Medical Communities* • *Informed Opinion or Assault?* • *More on Health Practitioners* • *The Contingency Fee* • *FDA—The 11th Myth*

MEDICINE IN AMERICAN HISTORY
174 *Abraham Lincoln and Cardiac Decompensation—A Preliminary Report* HAROLD SCHWARTZ, MD

THE HEALTH CARE TEAM
178 *Health Screening and the Role of Nurse Assistants—Medicolegal Considerations in California*
HENRY B. BRUYN, MD, and SUSAN CROCKER, MSW

INFORMATION
185 *Munchausen Syndrome Presenting as Urolithiasis*
WILLIAM A. JONES, MD; THOMAS P. COOPER, MD, and MARK D. KIVIAT, MD

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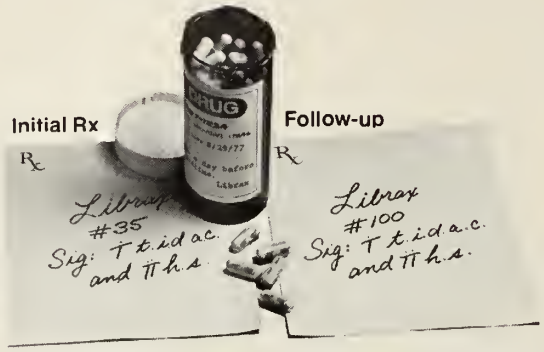

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Tel. (415) 765-5382 (collect)

B256

(H-1)

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First (Please Print or Type) Last

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STATE _____ ZIP _____ PHONE _____
(Area Code & No.)

† MEDICAL SCHOOL _____

‡ YEAR GRADUATED _____ DATE OF BIRTH _____

I AM INTERESTED IN (CHECK ONE):

- ☐ Flight Surgeon
- ☐ Undersea Medicine
- ☐ General Medical Officer
- ☐ Practicing My Specialty

*MY SPECIALTY (IF ANY) IS:

- ☐ Anesthesiology
- ☐ Family Practice
- ☐ Psychiatry
- ☐ Internal Medicine
- ☐ Neurology
- ☐ Radiology
- ☐ Pathology
- ☐ Pediatrics

STATUS ☐ (CHECK ONE):

- ☐ Private Practice
- ☐ Hospital Staff
- ☐ Intern
- ☐ Resident

WJM-2

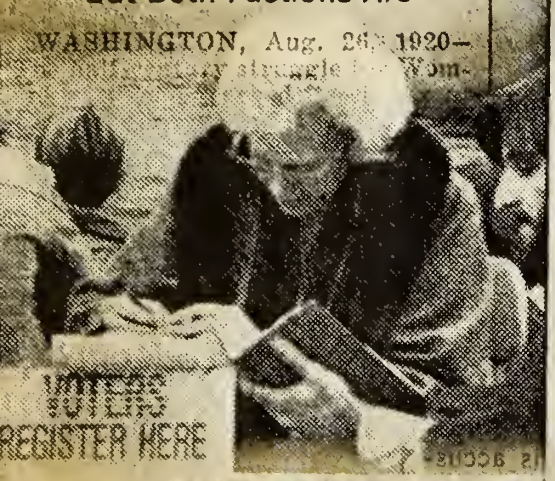
COLBY PROCLAIMS WOMAN SUFFRAGE

Signs Certificate of Ratification at His Home Without Women Witnesses.

MILITANTS VEXED AT PRIVACY.

Wanted Movies of Ceremony, But Both Factions Are

WASHINGTON, Aug. 26, 1920—



Social Security Bill Is Signed; Gives Pensions to Aged, Job

Roosevelt Approves Message Intended to Benefit 30,0 Persons When States Adopt Cooperating Laws—He the Measure 'Cornerstone' of His Economic Progra

WASHINGTON, Aug. 1 The Social Security Bill, p a broad program of unemp insurance and old age p and counted upon to bene 20,000,000 persons, becam day when it was signed b dent Roosevelt in the pre those chiefly responsible ting it through Co

Mr. Roosevelt cal "the cornerstone which is being me s comple ri to

SENATE APPROVES 18-YEAR OLD VOTE IN ALL ELECTIONS

Amendment to Constitution is Sent to House, Where Passage is Expected

WASHINGTON, March 10, 1971—The Senate approved today, 94 to 0, and sent to

TRUMAN CLOSES TED NATIONS CONFEREN ITH PLEA TO TRANSLATE CHARTER INTO DEEDS

NEW WORLD HOPE

President Hails 'Great Instrument of Peace,' Insists It Be Used

HISTORIC LANDMARK

Meeting Gives Standing Ovation as Executive Pictures Peace Gain

"If we fail to use it," he declared to the solemn final meeting of the delegates, 'we shall betray all of those who have died in order that we might meet here in freedom and safety to create it.'

"If we seek to use it selfishly—for the advantage of any one nation or any small group of nations—we shall be equally guilty of that betrayal."

Fervent Interpolation

The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session

SIGNI

the Draf Ends No

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Army that

PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

PMA
THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION
1155 FIFTEENTH ST. N W WASHINGTON, D C 20005

Clinical experience & continuing confidence

KAON® ELIXIR was introduced in **1954**, followed by KAON® TABLETS in **1963.** Decades of clinical experience indicate acceptability, effectiveness, and safety in the majority of patients; should abdominal pain occur, therapy should be discontinued. Both have been taken by patient after patient, day after day, year after year, to correct potassium deficiencies. Both have consistently demonstrated their value when diet alone is inadequate for potassium replacement.

Kaon® Elixir
(potassium gluconate)

Kaon® Tabs
(potassium gluconate)

BRIEF SUMMARY
Kaon Tablets/Kaon Elixir

KAON® (potassium gluconate) TABLETS

Description: Each sugar-coated tablet supplies 5 mEq. of elemental potassium (as potassium gluconate 1.17 Gm.). Kaon Tablets are sugar coated, not enteric coated, which favors dissolution in the stomach and absorption before reaching the small intestine where the lesions with enteric potassium chloride have occurred. The sugar coating merely adds to palatability and ease of swallowing, not to delay absorption as does the enteric coating.
Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. It may be used in the treatment of cardiac arrhythmias due to digitalis intoxication.
Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.
Warning: There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides or certain other oral diuretics. These small-bowel lesions have caused obstruction, hemorrhage and perforation. Surgery was frequently required and deaths have occurred. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Coated potassium tablets should be used only when adequate dietary supplementation is not practical.
Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient and periodic ECG and/or serum potassium levels should be made. High serum concentra-

1954
1978

Time is the test of all things

tns of potassium ion may cause death through c diac depression, arrhythmias or arrest. This dig should be used with caution in the presence cardiac disease.

n hypokalemic states, especially in patients c a salt-free diet, hypochloremic alkalosis is a ssibility that may require chloride as well as assium supplementation. In these circumsnces, Kaon (potassium gluconate) should be plemented with chloride. Ammonium chlore is an excellent source of chloride ion (18.7 q. per Gram), but it should not be used in tients with hepatic cirrhosis where ammonium sts are contraindicated. Other sources for oride are sodium chloride and Diluted drochloric Acid, U.S.P.

t should also be kept in mind that ammonium le cation exchange resin, sometimes used to at hyperkalemia, should not be administered to patients with hepatic cirrhosis.

Adverse Reactions: Nausea, vomiting, diarrhea and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

KAON® (potassium gluconate) ELIXIR

Description: Each 15 ml. (tablespoonful) supplies 20 mEq. of elemental potassium (as potassium gluconate, 4.68 Gm.) with saccharin and aromatics. Alcohol 5%.

Indications: See Kaon Tablets.

Precautions: See Kaon Tablets.

In hypochloremic alkalosis, potassium replacement with potassium chloride (e.g., Kaochlor® 10% Liquid) may be more advantageous than with other potassium salts.

Adverse Reactions: See Kaon Tablets.

Overdosage: See Kaon Tablets.

WARREN-TEED
LABORATORIES, INC.
DIVISION OF **ADRIA LABORATORIES INC.**
COLUMBUS, OHIO 43215

California Medical Association
107th Annual Session
Atop Nob Hill
March 17-22, 1978
San Francisco

SPECIAL PROGRAM

Tell it to the FDA

Saturday, March 18, 1978

2:00 to 5:00 p.m. • Masonic Temple Auditorium

The Food and Drug Administration is genuinely interested in establishing communication with practicing physicians. At the CMA Annual Session, high-level representatives of the FDA will conduct an open meeting with interested members of the CMA to foster this communication. Physicians are at the interface where the actions or interactions of the FDA have an effect upon patient care. This is an opportunity to "Tell it to the FDA."

Just Published!

THE MAKING OF A MEDICARE DOCTOR

By John M. Lanham, MD

The devastating story of how a Medicare physician must compromise his principles in order to continue to function within the bureaucratic system that demands such compromise. Reviews the implications of the current malpractice crisis and the bureaucracy in control of the free-enterprise system. **$5.95**

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Tablets

Percodan® (II)

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg. oxycodone terephthalate (WARNING: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

Endo Inc.
Manati, Puerto Rico 00701
Subsidiary of Endo Laboratories, Inc.
Subsidiary of the DuPont Company

DUPONT

CONSIDERATIONS FOR ORAL NARCOTIC ANALGESIC USE:

1. Determine need

What is causing pain? How is it perceived by you and your patient?

2. Prescribe a rapid-acting agent

Select a readily-absorbed oral agent that usually acts within 15 to 30 minutes.

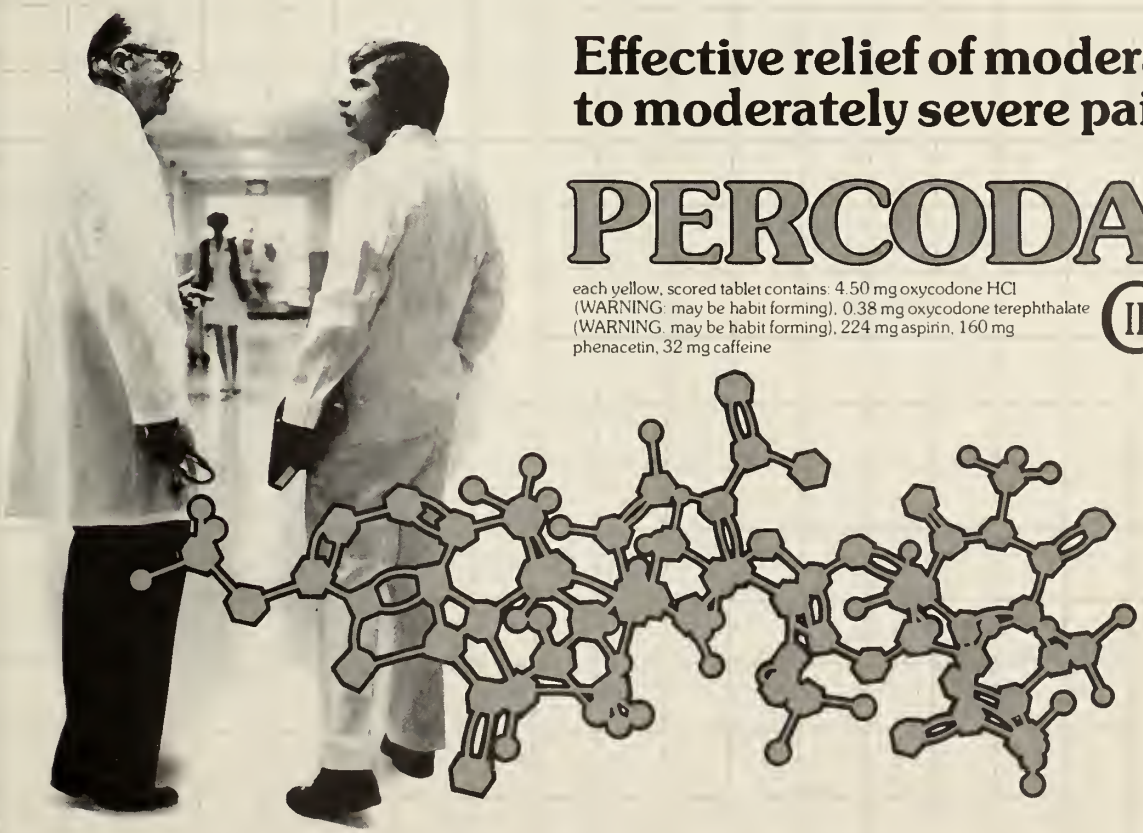
3. Minimize potential risk

Prescribe in limited quantities for selected patients.

Schedule II classification means no refills, no telephone Rx. Patients with persistent pain must return for your evaluation of analgesic needs.

4. Provide adequate analgesia with minimum doses

Consider PERCODAN® because patients rarely ask for increased dosage. PERCODAN® relief can last up to six hours–until time for next tablet.



Effective relief of moderate to moderately severe pain

Tablets

PERCODAN®

each yellow, scored tablet contains: 4.50 mg oxycodone HCl (WARNING: may be habit forming), 0.38 mg oxycodone terephthalate (WARNING: may be habit forming), 224 mg aspirin, 160 mg phenacetin, 32 mg caffeine

CII

PERCODAN® is a registered trademark of Endo Inc.

Please see facing page for Brief Summary of prescribing information.

If the Western Journal didn't exist,

Someone would have to invent it.

The Western Journal of Medicine fills several important needs. It's an especially useful and practical journal for physicians in practice. Also, it provides unique coverage of social and economic trends affecting medicine (the current issue is a good example). And, not least important, it's a voice for medicine in the West. Medical achievements in the Western states are brought to the attention of the profession at large and communication is maintained among Western physicians.

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BRETHINE®
erbutaline sulfate
A second wind
for asthmatics
Prescribing information is summarized on
he back of this page.

BRETHINE®
terbutaline sulfate

Geigy

It could mean a more active life for patients with reversible obstructive airways disease.

More effective
Brethine was more effective and longer acting than metaproterenol in a study of five patients with exercise-induced asthma.

Brethine has been shown to be highly effective alone and in combination with theophylline.

And Brethine has been shown to be twice as effective as ephedrine.

Long acting
Effect may last from 6 to 8 hours. One tablet at bedtime, upon arising and at midafternoon should keep patients breathing comfortably.

Minimal cardiac effect
Brethine produces proportionally greater changes in pulmonary function than in heart rate or blood pressure.

Tablets of 2.5 mg and 5 mg.
Some patients may experience mild hand tremor or "shakiness" when Brethine therapy is initiated. This may be minimized by starting patients with 2.5 mg doses.

Brethine®, brand of terbutaline sulfate, Tablets 5 mg., Tablets 2.5 mg. *Before prescribing or administering, please consult complete product information, a summary of which follows:*

Tablets contain 5 mg. (equivalent to 4.1 mg. of free base) or 2.5 mg. (equivalent to 2.05 mg. of free base) of Brethine, brand of terbutaline sulfate.

Indications: As a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Contraindications: Known hypersensitivity to sympathomimetic amines.

Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child.

Usage in Pediatrics. Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, and hyperthyroidism. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias. Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy.

Adverse Reactions: Commonly observed side effects include nervousness and tremor. Other reported reactions include headache, increased heart rate, palpitations, drowsiness, nausea, vomiting, and sweating. These reactions are generally transient in nature, usually do not require treatment, and appear to diminish in frequency with continued therapy. In general, all the side effects observed are characteristic of those commonly seen with sympathomimetic amines.

How Supplied: Round, scored, white tablets of 5 mg. in bottles of 100 and 1,000 and Unit Dose Packages of 100; oval, scored, white tablets of 2.5 mg. in bottles of 100.
(B) 98-146-060-E (Rev. 4/76)667004 C76-12

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

Brethine: alone or with theophylline, a second wind for asthmatics.

BR12820

Personally, Steve could never speak up for milk.

In TV commercials, you'll often see people speaking up for milk. Steve Allen and his wife Jayne Meadows are also seen on TV telling viewers about Mocha Mix... 100% milk free!

Matter of fact, this non-dairy creamer would have been found in their home way before they ever filmed the Mocha Mix series of commercials. Steve is allergic to milk products. Yet, he likes the splash of luxury and fresh taste in his coffee, on cereal, fruit and dessert, even in cooking. For the Allen household, Mocha Mix is the perfect answer.

It could well be the answer for many people who rely on you for their dietary needs, those with an allergy similar to Steve's, or a lactose intolerance. And, for many who must maintain a fat-restricted diet you should know that Mocha Mix is one non-dairy creamer that contains no coconut oil, giving it the highest ratio of unsaturated to saturated fat of any creamer. It easily exceeds the accepted standard 2:1 ratio. It's 100% cholesterol free, too. No wonder Mocha Mix is not just another non-dairy creamer, but the one you can rely on most for your patients who can't speak for milk, either.

NUTRITION INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)
Servings Per Container 16
Calories 40
Protein ..... 0 grams
Carbohydrate ..... 3 grams
Fat ..... 3 grams
Percent of Calories from Fat 73%
Polyunsaturated Fat .. 1 gram
Saturated Fat ..... 0 grams
Cholesterol (Δ) ..... 0 mg (0 mg/100g)

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to: Mocha Mix Dept. Presto Food Products, Inc. P.O. Box No. 21908, Los Angeles, Calif. 90021

Percentage of U.S. Recommended Daily Allowance (U.S. RDA)*

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

ΔInformation on fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

mocha mix®

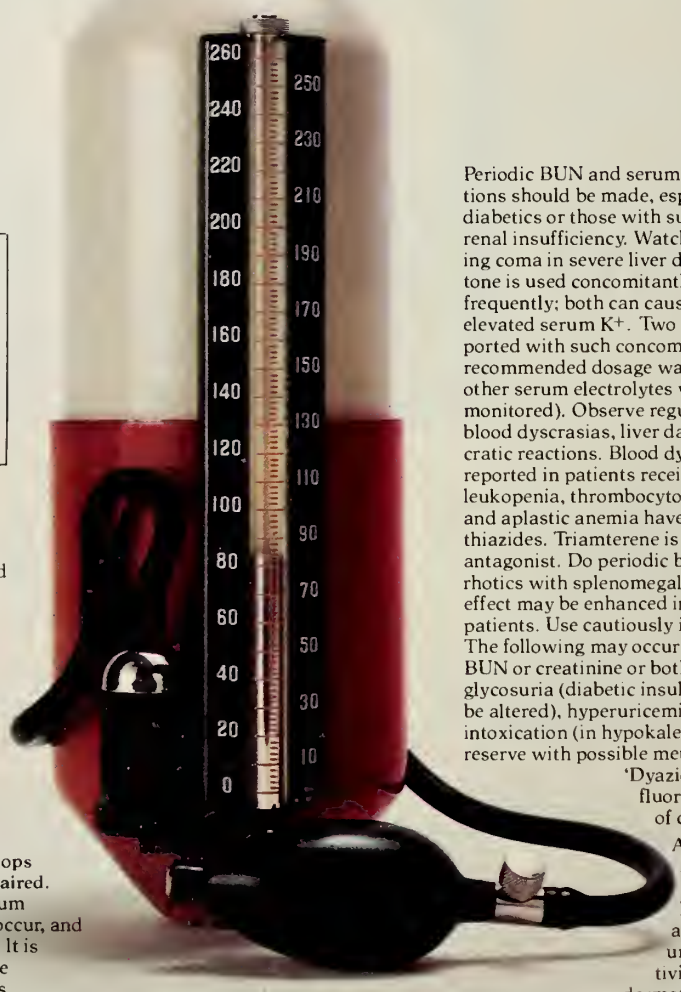
... the non-dairy creamer that's lowest in saturated fat.

TRIAMTERENE CONSERVES POTASSIUM WHILE HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F Co.) and 25 mg. of hydrochlorothiazide.

MAKES SENSE



Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* Warning
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

FOR LONG-TERM CONTROL OF HYPERTENSION.* SERUM K^+ AND BUN SHOULD BE CHECKED PERIODICALLY. (SEE WARNINGS SECTION.)

SK&F CO., Carolina, P.R. 00630

SK&F CO.
a SmithKline company

Simple drops of water help make COLACE® the most widely used stool softener.
COLACE®
dioctyl sodium sulfosuccinate
COLACE works by stool-softening action alone, free from laxative stimulation. Simply by letting natural intestinal water permeate stools, COLACE helps to eliminate the hard, dry stools common to constipation.
COLACE works to prevent pain and straining at stool with minimum chance of griping or cramps, particularly in patients with delicate anorectal disorders. COLACE is safe and non-habit forming in short- or long-term therapy. COLACE—the simple water way to ease constipation from infancy to old age. Capsules, syrup or liquid.
Mead Johnson PHARMACEUTICAL DIVISION

COMPATIBILITY

Eastern Tiger Swallowtail Butterfly
(Papilio glaucus)

Does it influence your choice of a peripheral/cerebral vasodilator*?

Vasodilan—compatible with coexisting diseases (e.g., glaucoma, diabetes)

Vasodilan has not been reported to affect the course of coexisting disease; it has not been reported to affect blood sugar levels or to raise intraocular pressure.

Vasodilan—compatible with concomitant therapy

Vasodilan has not been reported to affect the treatment of coexisting disease; it is compatible with such drugs as hypoglycemics and miotics.

Vasodilan—compatible with your total regimen for vascular insufficiency

Vasodilan can be a valuable adjunct in planning a total therapeutic program for vascular insufficiency.

***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg. Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

Dosage and Administration: Oral: 10 to 20 mg., three or four times daily. Intramuscular: 5 to 10 mg (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Parenteral administration is not recommended in the presence of hypotension or tachycardia.

Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted.

Administration of single dose of 10 mg. intramuscularly may result in hypotension and tachycardia. These symptoms are more pronounced in higher doses. For these reasons single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed.

Supplied: Tablets, 10 mg., bottles of 100, 1000, 5000 and Unit Dose; Tablets, 20 mg., bottles of 100, 500, 1000, 5000 and Unit Dose; Injection, 10 mg. per 2 ml. ampul, box of six 2 ml. ampuls.

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Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea and vomiting. The frequency of adverse reactions is related to the serum theophylline level and are not usually a problem at serum theophylline levels below 20μg/ml.
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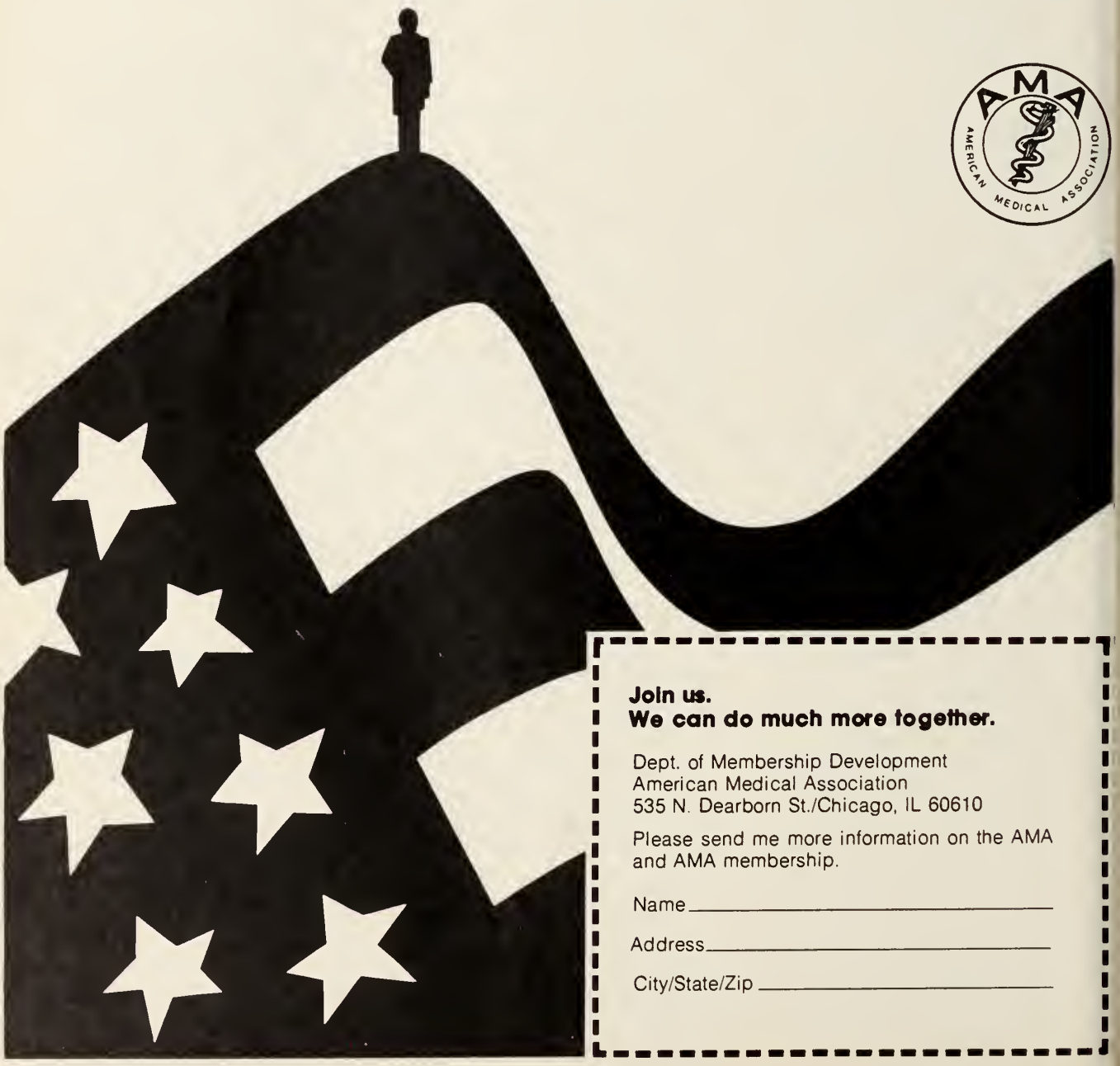

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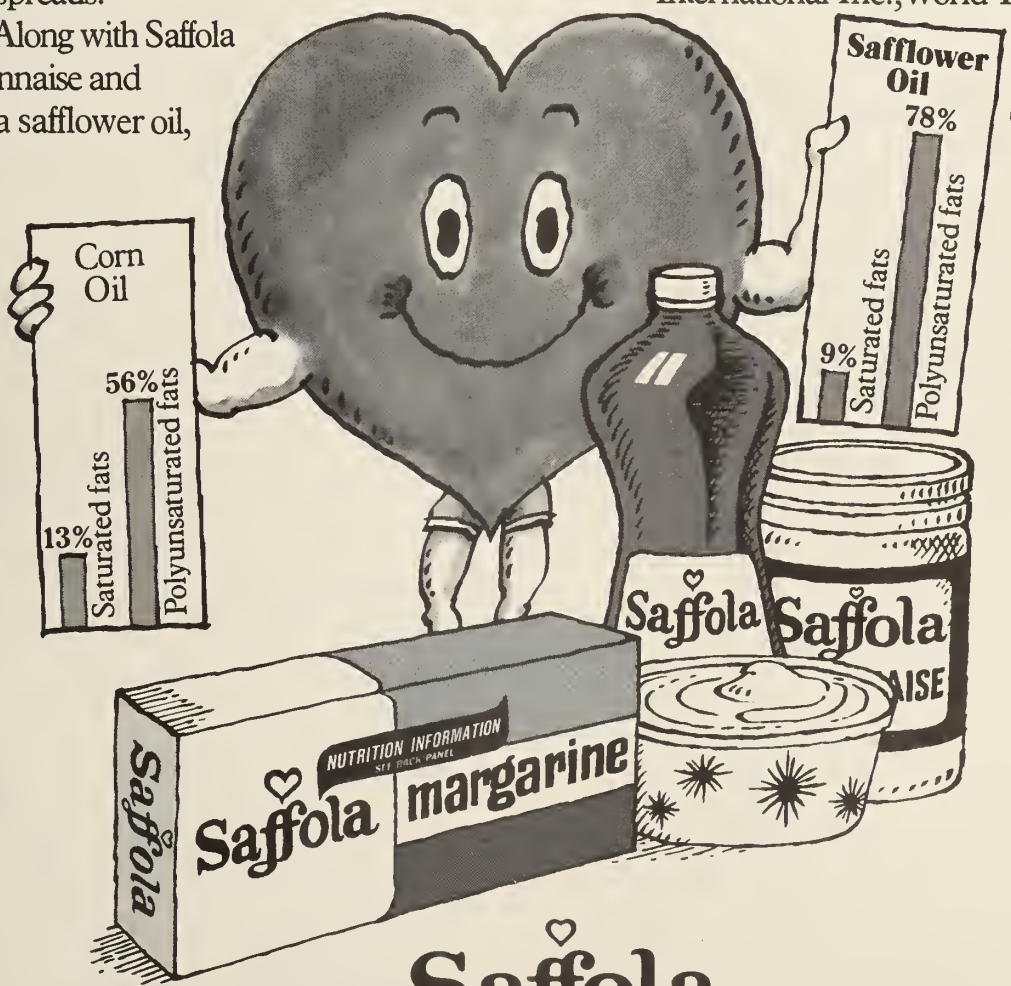

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CRITICAL CARE — 1978

Friday, March 3, 1978
8:00 AM – 5:00 PM

HOLIDAY INN
21333 Hawthorne Blvd.
Torrance, California 90503

Saturday, March 4, 1978
9:00 AM – NOON

GUEST FACULTY

Bernard Lown, M.D.

Michael Criley, M.D.
Richard Glassock, M.D.

Lucien Guze, M.D.
Paul Selecky, M.D.

H. J. C. Swan, M.D.
Max Harry Weil, M.D.

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ANESTHESIOLOGY

March 12-17—**Anesthesiology 1978—4th Annual Winter Meeting.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Mammoth Lakes. Sunday-Friday. 20 hrs. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA Sch. of Med., Los Angeles 90024.

March 19-23—**International Anesthesia Research Society—52nd Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: B. B. Sankey, MD, IARS, 3645 Warrensville Center Rd., Cleveland OH 44122. (216) 295-1124.

April 16-21—**California Society of Anesthesiologists—2nd Hawaii Seminar.** Hyatt Regency Hotel, Waikiki-Honolulu. Sunday-Friday. 20 hrs. Contact: CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 6-7—**American Society of Anesthesiologists Workshop.** St. Francis Hotel, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

June 1-4—**California Society of Anesthesiologists—Annual Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401.

CANCER

March 4—**What's New in Oncology 1978.** American Cancer Society at San Joaquin Delta College, Stockton. Saturday. 6 hrs. $20. Contact: Karen Schaefer, 1111 W. Robinhood Dr., Stockton 95207. (209) 477-2676.

March 6-9—**National Conference on the Detection and Treatment of Breast Cancer.** American College of Radiology at Hyatt Regency Hotel, San Francisco. Monday-Thursday. 29 hrs. Contact: Breast Cancer Conf., ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015.

March 8—**Carcinoma of the Breast.** LLU. Wednesday. 4 hrs. $25.

March 9-12—**Modern Concepts in Oncology.** UCLA at Canyon Hotel, Palm Springs. Thursday-Sunday.

March 10-11—**Medical and Therapeutic Complications in Patients With Malignant Diseases.** Eisenhower Med. Center at Erawan Garden Hotel, Indian Wells. Friday-Saturday. 10 hrs. $50. Contact: John J. Deller, MD, Dir. of Education and Research, EMC, 39000 Bob Hope Dr., Palm Desert 92260.

March 17—**Cancer of the Lung.** California Hospital Medical Center, Los Angeles. Friday. 5 hrs. $15. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 27-31—**Cancer.** STAN. Monday-Friday. 27 hrs. $265.

May 10—**Carcinoma of the Cervix: Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $25.

June 19-23—**Head and Neck Oncology.** UCLA. Monday-Friday.

June 30-July 1—**International Endocurietherapy Symposium.** USC at Hotel Bonaventure, Los Angeles. Friday-Saturday. 22 hrs.

EMERGENCY MEDICINE

February 26-March 3—**Emergency Medical Care Symposium II.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. $175.

March 20-24—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

April 3-7—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

April 15-22—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $300.

May 8-12—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

May 8-13—**Topics in Emergency Medicine,** UCSF at Ralph K. Davies Med. Center, San Francisco. Monday-Saturday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—Callfornia College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

May 10-12—**Emergency Room Radiology.** See Radiology, May 10-12.

June 3-4—**Critical Care Monitoring.** UCLA at Airport Marina Hotel, Marina Del Rey. Saturday-Sunday.

July 24-28—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

MEDICINE

February 15-17—**Topics in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 22-24—**Daily Decisions in Lung Diseases.** Calif. Thoracic Society at Balboa Bay Club, Newport Beach. Wednesday-Friday. Contact: Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 23-25—**Advances in the Diagnosis and Therapy of Cardiovascular Disease—1978.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 25—**Annual Cardiology Symposium.** Fresno Community Hospital. Saturday. 7 hrs. Contact: Joanne Ellis, Fresno Community Hospital, P. O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

March 3—**Diabetes Program—5th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday.

March 3-4—**Diagnosis and Management of Aphasia.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 12 hrs. $100.

March 6-9—**American College of Cardiology—27th Annual Scientific Session.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: Patrick Ziarnik, Dir., Annual Sci. Session Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 6-May 22—**How To Read Your Own EKG's—Workshop in Practical Electrocardiology.** Memorial Hospital Medical Center, Long Beach. Monday evenings; 24 hrs. $240. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 10-11—**Clinical Cardiology.** American College of Cardiology at Kauai Surf Hotel, Kauai, Hawaii. Friday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 16-19—**Viral Hepatitis.** UCSF at Hilton Hotel, San Francisco. Thursday-Sunday. 26 hrs. $145.

March 17-18—**American College of Physicians—Nevada/Northern California Regional Meeting.** Mark Hopkins Hotel, San Francisco. Friday-Saturday. Contact: Ralph O. Walerstein, MD, FACP, 3447 Clay St., San Francisco 94118.

March 23-25—**Immunology and Allergy Conference—2nd Annual.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

March 28-31—**Consultant's Course in Dermatology—6th Annual.** UCSF. Tuesday-Friday. 25½ hrs. $250.

March 31-April 1—**Seminar on Thrombosis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 9 hrs. $75.

April 1-6—**American College of Allergists—34th Annual Congress.** Hilton Hotel, Las Vegas. Saturday-Thursday. 30 hrs. $75, ACA members; $190, nonmembers. Contact: Frances P. White, ACA, 2141 14th St., Boulder, CO 80302. (303) 447-8111.

April 3-12—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 3-14—**Intensive Review of Internal Medicine.** USC. 12 days.

April 12-June 14—**Nephrology for the Practicing Internist.** UCLA. Wednesday evenings; 10 weeks.

April 14-15—**Operative Arthroscopy.** See Surgery, April 14-15.

April 15-22—**Chronic Obstructive Pulmonary Disease—From the Beginning to the End.** International Center for Postgraduate Medical Education at Kona Surf Hotel, Hawaii. One week. 25 hrs. Contact: Ms. Kym Westenberg, ICPME, 3969 Cuervo, Santa Barbara 93110. (805) 967-0497.

April 19-21—**Echocardiographic Solutions to Clinical Cardiovascular Problems.** American College of Cardiology and UCLA at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 24-29—**American Academy of Neurology — Annual Meeting.** Bonaventure Hotel, Los Angeles. Monday-Saturday. $35, members; $55, nonmembers. Contact: Mr. Stanley A. Nelson, Exec. Dir., AAN, 4015 W. 65th St., Suite 302, Minneapolis, MN 55435. (612) 920-3636.

May 1—**Current Problems in Neuromuscular Disease.** PMC at Hyatt on Union Square, San Francisco. Monday. 6 hrs. $95.

May 4-5—**Current Concepts in Medicine: Stroke.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 13 hrs. $200.

May 4-7—**American Society of Internal Medicine — Annual Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. Contact: ASIM, 535 Central Tower Bldg., 703 Market St., San Francisco 94103. (415) 777-1000.

May 13—**Controversies in Internal Medicine—2nd Annual.** San Jose Hosp. and Health Center, Inc., at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $35. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 16—**Common Skin Problems Seen in Office Practice.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, 199 E. Webster St., Colusa 95932. (916) 458-5844.

May 19—**American Heart Association, California Affiliate—Physicians' Scientific Sessions.** Vacation Village, San Diego. Friday. Contact: Marilyn Probst, AHA, Calif. Affiliate, 805 Burlway Rd., Burlingame 94010. (415) 342-5522.

May 19—**The Child With Heart Disease: The Practitioner's Role.** See Pediatrics, May 19.

May 20—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

May 22-26—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

June 14—**Acute and Chronic Diarrhea.** LLU. Wednesday. 4 hrs. $25.

June 15-17—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Bahia Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

OBSTETRICS AND GYNECOLOGY

February 15-19—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Of Interest To All, February 15-19.

March 9-10—**Gynecological Urology Seminar.** See Surgery, March 9-10.

March 31-April 1—**Obstetrics/Gynecology—Annual Symposium.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Symposium Coordinator, SCPMG, 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027.

April 10-12—**Antenatal Assessment of the Fetus From Conception to Delivery.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $150.

April 13-15—**Basic Colposcopy/Ob-Gyn.** UCD at Sacramento Inn, Sacramento. Thursday-Saturday.

PEDIATRICS

February 15—**Pediatric Hematology.** LLU. Wednesday. 8 hrs. Contact: Sanford Schneider, MD, A531, LLU Med. Ctr., Loma Linda 92354. (714) 796-7311, ext. 2832.

February 18—**Currents in Pediatric Endocrinology.** Memorial Hospital Medical Center, Long Beach. Saturday. 4 hrs. $35. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 23-25—**Development in Infancy and Childhood—Annual Winter Meeting.** Children's Hospital Med. Ctr., Oakland, at Sahara Tahoe Hotel, So. Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, CHMC, 51st and Grove Sts., Oakland 94609.

February 24-26—**Recent Advances in Patterns of Infant Development: Relevance for Later Life.** So. Calif. Soc. for Child Psychiatry; Com. on Psychiatric Dimensions of Infancy, AACP; Chap. 2, ACP, at South Coast Plaza Hotel, Costa Mesa. Friday-Sunday. 18 hrs. Contact: SCSCP, 14724 Ventura Blvd., No. 604, Sherman Oaks 91403. (213) 986-8066.

March 17-19—**Combined Southern California Pediatric Postgraduate Meeting—8th Annual.** American Academy of Pediatrics, District IX, Chapter 2, at Riviera Hotel, Palm Springs. Friday-Sunday. $135, members; $150, non-members. Contact: Calif. Chapter 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 5-7—**General Pediatrics.** American Academy of Pediatrics at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 7-8—**Common Problems in Ambulatory Pediatrics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9½ hrs. $50.

April 8-13—**American Academy of Pediatrics—Spring Session.** Century Plaza Hotel, Los Angeles. Saturday-Thursday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

May 1-5—**Pediatric Review.** USC. Monday-Friday.

May 11-13—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 13-20—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 28 hrs. $300.

May 19—**The Child With Heart Disease: The Practitioner's Role.** UCD at Woodlake Inn, Sacramento. Friday. 6 hrs.

May 20-21—**Neuropediatrics.** UCLA. Saturday-Sunday. 11 hrs. $165.

May 27-29—**American Academy of Pediatrics, California Chapter I, District IX.** Hyatt House, Monterey. Saturday-Monday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

PSYCHIATRY

March 4-5—**Clinical Psychopharmacology.** Cedars-Sinai Medical Center, Los Angeles. Saturday-Sunday. 9 hrs. $125. Contact: Ms. Lore Kane, CME, Rm. 2049, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

March 11—**Update in the Diagnosis and Treatment of Personality Disorders.** UCD. Saturday. 6 hrs. $45.

March 11-12—**Hypnosis and Behavior Modification: Imagery Conditioning.** DREW at Airport Marina Hotel, San Francisco. Saturday-Sunday. $200; $100, residents and interns.

March 11-12—**Managing the Psychosocial Needs of the Physically Ill.** See Of Interest To All, March 11-12.

March 27-31—**American Orthopsychiatric Association—55th Annual Meeting.** Hilton Hotel, San Francisco. Monday-Friday. 12 hrs. Contact: Dr. Marion Langer, AOA, 1775 Broadway, New York 10019.

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25 HOURS CMA ACCREDITATION

April 15-16—**Stress: Psychological Management.** UCLA at Santa Cruz. Saturday-Sunday.

May 19-21—**Treatment of Schizophrenia.** UCSF. Friday-Sunday.

June 2-3—**Psychosocial Care of the Dying Patient.** See Of Interest To All, June 2-3.

June 26-30—**Comparative Psychotherapies.** USC. Monday-Friday.

RADIOLOGY AND PATHOLOGY

February 15-17—**Anaerobic Bacteriology Methods.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 11½ hrs. $80. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

February 19-24—**Interpretative Enzymology.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Friday. 25 hrs.

February 21—**Clinical Laboratory Tests: Results, Clinical Application and New Laboratory Tests.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

February 23-25—**Advanced Topics in Computerized Tomography (CT).** Memorial Hospital Medical Center, Long Beach. Thursday-Saturday. 15 hrs. $200. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

March 1—**Computerized Tomography—Dinner Meeting/Scientific Program.** LA Soc. of Internal Medicine at LA Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50. Contact: Thomas Yoshikawa, MD, LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

March 4-5—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 9 hrs. $100.

March 5-10—**Medical Imaging in the High Sierra.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Sahara Tahoe Hotel, Lake Tahoe. Sunday-Friday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

March 6-10—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 32 hrs. $275.

March 11-12—**A Practical Course in B-Scan Ultrasound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 9 hrs. $125.

April 9-14—**American College of Radiology—Annual Meeting and Categorical Course.** Town and Country Hotel, San Diego. Sunday-Friday. Contact: Ms. Sheila Aubin, Meeting Manager, ACR, 20 N. Wacker Dr., Chicago, IL 60606. (312) 236-4963.

May 4-5—**New Concepts in Medicine: Stroke.** See Medicine, May 4-5.

May 10-12—**Emergency Room Radiology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday. 15 hrs. $160.

May 12—**Radiology Symposium.** UCD at Red Lion Motor Inn, Sacramento. Friday. 7½ hrs. $50.

June 18-23—**Pathology of the Lung.** UCSD. Sunday-Friday, 50 hrs. $400.

July 30-August 5—**Medical Imaging.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Saturday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

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SURGERY

February 28-March 3—**Diagnosis and Management of Acoustic Neuromas and Skull Base Tumors.** Ear Research Institute, Los Angeles. Tuesday-Friday. 32 hrs. $400. Contact: William F. House, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 3-4—**Development and Management of Aphasia.** See Medicine, March 3-4.

March 6-17—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Fred H. Linthicum, MD, Dir. of Education, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

March 9-10—**The Orbit: Diagnostic Approaches and Management Decisions.** PMC at Stanford Court Hotel, San Francisco. Thursday-Friday. $225.

March 9-10—**Gynecological Urology Seminar.** American Urological Association at Airport Marina Hotel, Los Angeles. Thursday-Friday. 16 hrs. $180. Contact: Gynecological Urology Seminar, c/o Joseph J. Kaufman, MD, UCLA Med. Ctr., Div. of Urology, Los Angeles 90024.

March 11—**Cataract Surgery and Intraocular Lens.** Jules Stein Eye Institute and UCLA. Saturday. 8 hrs. $225. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

March 17-18—**Ophthalmology Update V.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $225.

March 21—**Urology—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 28-April 1—**Controversial Areas in Surgery—15th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Tuesday-Saturday. 16 hrs. $230.

March 30-31—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs.

April 1-5—**Vascular Surgery—6th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

April 7-8—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

April 12-14 — **Maxillofacial Trauma Symposium.** UCSF. Wednesday-Friday.

April 13-15—**General Surgery—Annual Course.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 14-15—**Operative Arthroscopy.** UCLA. Friday-Saturday. 12 hrs. $315.

April 15-22—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 18—**Orthopaedics—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

April 20-21—**Current Concepts of Macular Structure, Function and Disease—9th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute and UCLA at Century Plaza Hotel, Los Angeles. Thursday-Friday. $225. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

April 20-21—**Current Problems in Intensive Care: The Cardiac Surgical Patient.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 11 hrs. $125.

April 29-May 6—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $275.

May 1-12—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Fred H. Linthicum, MD, Dir. of Education, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

May 4-5—**New Concepts in Medicine: Stroke.** See Medicine, May 4-5.

May 6—**Flexible Bronchofibroscopy.** PMC. Saturday. 6 hrs. $300.

May 6—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 11-12—**Office Orthopedics.** USC. Thursday-Friday.

May 18-20—**Neurosurgery.** UCSF at Sheraton Palace, San Francisco. Thursday-Saturday.

June 2-3—**Intraocular Lens Implantation Course.** Santa Monica Hospital. Friday-Saturday. $600. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

June 9-10—**Ophthalmology Update VI.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 6 hrs. $225.

June 10—**Strabismus Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 11-15—**American Society of Colon and Rectal Surgeons—Annual Convention.** San Diego. Sunday-Thursday. Contact: Harriette Gibson, Admin. Sec., ASCRS, 615 Griswold, No. 516, Detroit, MI 48226. (313) 961-7880.

June 15-17—**Hip Course.** UCLA. Thursday-Saturday.

June 15-17—**Highlights of Ophthalmology.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday. 16 hrs. $195.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

February 15-17—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hospital and Med. Ctr., P. O. Box 7921, San Francisco 94120. (415) 567-6600, ext 2401.

February 15-19—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** Tyler Med. Clinic and Century City Hosp. at Hilton Hotel, Las Vegas. Wednesday-Sunday. Contact: Jaroslav J. Marik, MD, 921 Westwood Blvd., Los Angeles 90024.

February 16-17—**Selected Topics in Geriatric Medicine.** STAN and Palo Alto VA Hospital at Stanford. Thursday-Friday.

February 19-24—**Caring for Older Persons.** Medical Communications and Services Assn. at Kona Surf Hotel, Kailua, Kona, Hawaii. Sunday-Friday. 31 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

February 22-24—**Daily Decisions in Lung Diseases.** Calif. Thoracic Society at Balboa Bay Club, Newport Beach. Wednesday-Friday. $150, members; $175, nonmembers. Contact: Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 25-26—**National Symposium on Aging.** UCSF. Saturday-Sunday.

February 26-March 3—**Clinical Management of Sexual Problems.** Medical Communications and Services Assn. at Sheraton Hotel, Molokai, Hawaii. Sunday-Friday. 30 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

February 27-March 3—**Basic Science for Clinicians.** STAN. Monday-Friday. 25½ hrs. $265.

March 3-4—**Diagnosis and Management of Aphasia.** See Medicine, March 3-4.

March 3-5—**Resources in Human Sexuality.** National Sex Forum; Institute for Advanced Study of Human Sexuality; San Diego Society for Sex Therapy and Education at Hilton Hotel, San Diego. Friday-Sunday. 15 hrs. $110. Contact: Cont. Ed., Nat'l Sex Forum, 1523 Franklin St., San Francisco 94109. (415) 928-1133 or (213) 990-0774.

March 4-5—**Current Trends in the Management of Common Genetic Disorders.** UCLA. Saturday-Sunday.

March 4-5—**Clinical Psychopharmacology.** See Psychiatry, March 4-5.

March 6-8—**Diagnosis, Treatment and Prevention of Genetic Disease.** American College of Physicians; Harbor Gen. Hospital; Nat'l Foundation-March of Dimes at Riviera Hotel, Palm Springs. Monday-Wednesday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia 19104.

March 7-May 23—**Bedside Clinics.** USC at Children's Hospital, Los Angeles. Tuesday evenings.

March 8-10—**Neurology for Non-Neurologists.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday. 22 hrs. $250.

March 10-12—**American Medical Association—Regional Seminar.** Newporter Inn, Newport Beach. Friday-Sunday. Contact: G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

March 11-12—**Managing the Psychosocial Needs of the Physically Ill.** UCLA. Saturday-Sunday. 14 hrs.

March 14-18—**Sports Medicine for the Primary Physician.** Univ. of Hawaii School of Medicine at Princess Kaiulani Hotel, Honolulu. Tuesday-Saturday, 18 hrs. $200. Contact: Univ. of HI Sports Medicine Course, Hawaii Conference Services, P.O. Box 22670, Honolulu 96822.

March 15-18—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Wednesday-Saturday.

March 17-19—**Family Practice—Intensive Review.** DREW. Friday-Sunday.

March 17-22—**California Medical Association—107th Annual Session.** Fairmont Hotel, San Francisco. Friday-Wednesday. Contact: Linda Ramsey, CMA.

March 25—**Burn Care for the Non-Burn Physician.** Alta Bates Hospital, Berkeley. Saturday. Contact: Dept. of Medical Education, Alta Bates Hosp., 1 Colby Plaza, Berkeley 94705. (415) 845-7110, ext. 2055.

April 2-7—**Electrophysiology.** USC at Erawan Gardens, Palm Springs. Sunday-Friday.

April 6-8—**West Coast Counties Postgraduate Institute.** CMA at Sunset Convention Center, Carmel. Thursday-Saturday. Contact: Richard Manley, CMA.

April 6-9—**Basic Clinical Hypnosis—2nd Annual Workshop.** UCI and Orange Co. Society of Clinical Hypnosis at Balboa Bay Club, Newport Beach. Thursday-Sunday. 23 hrs. $275. Contact: Univ. Extension, Fee and Information Office, Rm. 102 Admin. Bldg., UCI, Irvine 92717.

April 7-9—**Resources in Human Sexuality.** National Sex Forum; Institute for Advanced Study of Human Sexuality; and San Diego Soc. for Sex Therapy and Education at Hilton Hotel, San Diego. Friday-Sunday. 15 hrs. $110. Contact: Cont. Ed., Nat'l Sex Forum, 1523 Franklin St., San Francisco 94109. (415) 928-1133 or (213) 990-0774.

April 8-9—**Stress: Medical Management.** UCLA at Palm Springs. Saturday-Sunday. 14 hrs.

April 12—**The Prostate.** LLU. Wednesday. 4 hrs. $25.

April 17-19—**Stress Workshop.** UCLA at Yosemite. Monday-Wednesday. 15 hrs.

April 22-23—**Practical Dermatology for the Primary Care Physician.** UCLA. Saturday-Sunday.

April 22-29—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 27-29—**San Joaquin Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Richard Manley, CMA.

April 28-30—**Therapeutic Decision Making.** PMC at Pajaro Dunes, Watsonville. Friday-Sunday. 15 hrs. $300.

April 29-30—**Sports Medicine.** UCLA. Saturday-Sunday.

May 12-13—**Alumni Days.** UCSF. Friday-Saturday.

May 12-14—**Resources in Human Sexuality.** National Sex Forum and Institute for Advanced Study of Human Sexuality at Towne House, Fresno. Friday-Sunday. 15 hrs. $110. Contact: Cont. Ed., Nat'l Sex Forum, 1523 Franklin St., San Francisco 94109. (415) 928-1133 or (213) 990-0774.

May 13—**Clinical Pharmacology.** STAN and Palo Alto Medical Clinic at STAN. Saturday. $15.

May 15-21—**Diving Medicine.** UCSF at VA Hospital, Fresno. One week.

May 19-21—**Health Aspects of Human Sexuality.** Human Sexuality Program, UCSF. Friday-Sunday. Contact: John Holland, Human Sexuality Prog., UCSF, 350 Parnassus Ave., Suite 700, San Francisco 94143. (415) 666-4787.

May 21-26—**Orthopaedic Symposium for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $225.

June 2-3—**Management of Medical Problems.** PMC. Friday-Saturday. 15 hrs.

June 2-3—**Psychosocial Care of the Dying Patient.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

June 7-9—**Dermatology for the Family Practitioner.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Friday. 14½ hrs. $100.

June 8-10—**Nutritional Care of the Hospitalized Patient.** UCSF. Thursday-Saturday.

June 10-11—**San Diego Chapter, California Academy of Family Physicians—22nd Annual Postgraduate Symposium.** Town and Country Hotel, San Diego. Saturday-Sunday. Contact: Irene Adams, Exec. Sec., SDAFP, 4406 Alta Mira, La Mesa 92041. (714) 466-0770.

June 10-11—**Practical Infectious Diseases for the Primary Care Physician.** UCLA. Saturday-Sunday.

June 18-23—**Family Practice Refresher Course—9th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. Monday-Saturday.

June 20—**Hypertension—Rationale for Appropriate Work-Up and Advances in Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213.

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OPHTHALMOLOGY

March 17-18—**The Oregon Academy of Ophthalmology Annual Convention.** Sheraton Hotel, Lloyd Center, Portland. Contact: Rebecca Tarshis, Executive Secretary Oregon Academy of Ophthalmology, 918 NE 44th Ave., Portland 97213.

OF INTEREST TO ALL PHYSICIANS

March 2—**Circuit Course Program on Advances in Pediatrics.** St. Anthony Hospital, Pendleton. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

March 2—**Circuit Course on Disorders of the Lower GI Tract.** Albany General Hospital, Albany. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

March 2—**Circuit Course Program on Evaluation of the Severely Injured.** Josephine General Hospital, Grants Pass. Contact Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

March 10-11—**Carcinoma of the Colon and Its Management.** Salishan Lodge, Gleneden Beach. Contact: James H. Lium, MD, Tumor Registry, Salem Memorial Hospital, 665 Winter St. SE, Salem 97301.

March 31-April 1—**Oregon Heart Association Annual Meeting.** Red Lion, Portland. Contact: Oregon Heart Association, 1500 SW 12th, Portland 97205.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

February 13-16—**Pediatric Gynecology—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Monday, Feb. 13, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Tuesday-

Wednesday, Feb. 14-15, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, Feb. 15-16, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 14-17—**Oncology.** Tuesday-Friday. 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. Contact: College of Medical Education, University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

February 15—**Headaches—Univ. of Wash. General Medicine Sessions in Anacortes, Washington.** Contact: Harry Eiesland, MD, 24th and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

February 17-18—**Controversies in Obstetrics and Gynecology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

February 22-24—**Immunoglobulins and Immunologic Disaster —Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Feb. 22, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Feb. 23, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education. Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Feb. 24, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

February 23-24—**Lower Intestinal Diseases—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Feb. 23, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Feb. 24, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

March 3-4—**Hypertension Symposium.** Friday-Saturday. Big Sky, Montana. Contact: D. Frank Johnson, MD, Dir. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 3-4—**First Annual Montana OB-GYN Meeting.** Friday-Saturday. Big Sky, Montana. 6 hrs. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801.

March 3-5—**General Topics in Urology.** Friday-Sunday. Big Sky, Montana. 6 hrs. Contact: John Stone, MD, 2517 7th Ave. S., Great Falls, MT 59401. (406) 452-9546.

March 3-4—**Nephrology.** Friday-Saturday. Glasier Auditorium, Swedish Hospital and Medical Center, Seattle. Contact: Dept. of Med., Ed., Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2266.

March 6-10—**The Medical Model of the Future: Holistic Health.** Monday-Friday. Sun Valley, Idaho. 20 hrs. Fee: Physicians, $275; others, $225. Contact: Paulette Gregg, Box 992, Sun Valley, ID 83353. (208) 726-4248.

March 12-16—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Sunday-Monday, March 12-13, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. Tuesday-Wednesday, March 14-15, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, March 15-16, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 16-17—**Internal Medicine.** Thursday-Friday. Tacoma, Wash. Contact: Mrs. Maxine Bailey, College of Medical Education, University of Puget Sound, 1500 N Warner, Tacoma, WA 98416. (206) 756-3152.

March 17-18—**Surgery of the Liver and Biliary Tract.** Friday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

March 22-24—**Antibiotics and Infectious Disease—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, March 22, Great Falls. Contact: Mr. John Breeden, PO Box 2829 Great Falls, MT 59403. (406) 453-1493. Thursday, March 23, Billings. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, March 24, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

March 24-25—**Gynecologic Cancer.** Friday-Saturday. Glasier Auditorium, Swedish Hospital and Medical Center. Contact: Dept. of Med. Ed., Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2266.

March 27-28—**Premature Coronary Artery Disease and Lipoprotein—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, March 27, Wenatchee. Contact: William M. McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, March 28, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

March 30-31, April 6-7—**Endocrine Glands.** Thursdays-Fridays. 8 am-10 am, Good Samaritan Hospital, Puyallup, Wash. Contact: Mrs. Maxine Bailey, College of Medical Education, University of Puget Sound, 1500 N Warner, Tacoma, WA 98416. (206) 756-3152.

April 5, 12, 19, 26—**Potpourri.** Wednesdays, 8-10 a.m., Tacoma General Hospital, Tacoma, Washington. Contact: Mrs. Maxine Bailey, College of Medical Education, University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

April 9-13—**Pediatric Pulmonary Disease—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Sunday-Monday, April 9-10, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Tuesday-Wednesday, April 11-12, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, April 12-13, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 11-12—**Antibiotics Use in the Surgical Patient—Univ. of Wash. Surgical Program in Montana.** Tuesday, April 11, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59401. (406) 454-1493. Wednesday, April 12, Billings. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Wednesday, April 12, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

April 13-15—**Refresher Course in Diagnostic Radiology.** Thursday-Saturday. Sacred Heart Medical Center, Spokane, Washington. 6 hrs. Fee: $80. Contact: Mrs. Eunice Fisher, Dept. of Radiology, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-3330.

April 19—**Pacemaker Indications, Selection and Follow-up—Univ. of Wash. General Medicine Program in Anacortes, Washington.** Contact: Harry Eiesland, MD, 24th and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

April 24-25—**Gynecologic Oncology—Univ. of Wash. Obstetrics and Gynecology Program in Idaho and Washington.** Monday, April 24, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391. Tuesday, April 25, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 24-25—**Pulmonary Disease, Part II—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, April 24, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, April 25, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

April 26-28—**Interpretation of Cardiac Data, Valvular Heart Disease—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, April 26, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, April 27, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, April 28, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

Index to
The Western Journal of Medicine
Advertising

American Medical Association 26

Burroughs Wellcome Co.
Empirin Compound w/Codeine #3;
Empracet w/Codeine #3 3

Classified 22, 24, 25

"Tell It to the FDA," Special Program,
CMA Annual Session 10

Eli Lilly and Company
Kefzol/I.M./I.V. 21

Endo Inc.
Percodan 10, 11

Geigy Pharmaceuticals
Brethine 13, 14

International Center for Postgraduate Medical Education
Chronic Obstructive Pulmonary Disease 31

Mead Johnson Laboratories
Colace 17
Vasodilan 18, 19
Quibron 20

Medical World News 23

Navy Recruiting Area Eight 5

Pharmaceutical Manufacturers Association 6, 7

Presto Food Products Inc.
Mocha Mix 15

PVO International
Saffola 27

Roche Laboratories
Librax ..... 2nd Cover, 1, 2
Valium ..... 3rd and 4th Covers

Smith Kline & French Co.
Dyazide 16

Society for Continuing Medical Education
Symposium: Gynecologic Oncology 28

Sofredex, Pronuptia de Paris 36

South Bay Hospital Annual Medical Symposium
Critical Care—1978 28

Vantage Press Inc.
"The Making of a Medicare Doctor" 10

Warren-Teed Pharmaceuticals Inc.
Kaon Elixir-Kaon Tabs 8, 9

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THE WESTERN
Journal of Medicine

Refer to: Granoff DM, Basden M, Rockwell R: Ampicillin-resistant Hemophilus influenzae—Emergence in California's Central Valley. West J Med 128:101-105, Feb 1978

Ampicillin-Resistant Hemophilus influenzae

Emergence in California's Central Valley

DAN M. GRANOFF, MD; MILLIE BASDEN, RN, and RICHARD ROCKWELL, MA
Fresno, California

Ampicillin-resistant Hemophilus influenzae had not been identified in Fresno, California, before June 1976. In the 12 months that followed, eight resistant type B strains and three resistant nontypable isolates were cultured from patients treated at two hospitals that provide nearly all of the acute pediatric inpatient care for the area. Two of the resistant strains were obtained from patients with invasive infections and represented 4.2 percent of Hemophilus influenzae isolated from blood, cerebrospinal fluid or joint aspirates during the 12 months. The remaining six resistant type B strains were obtained from 117 patients, and were the predominant organism in cultures of other sites, primarily respiratory secretions.

In two of three patients infected with nontypable organisms, resistance appeared to emerge during therapy with ampicillin. Measurement of β lactamase was a practical and accurate method for differentiating between ampicillin-sensitive and resistant strains. All ten of the β lactamase-positive isolates tested had minimal inhibitory concentrations (MIC) for ampicillin of 15 μg per ml, or less. In contrast 30 β lactamase-negative strains had MIC's of 1.5 μg per ml, or less, of ampicillin. Our results indicate that ampicillin resistance has become a significant problem in the Central Valley of California and probably the entire state.

CASES OF ampicillin-resistant Hemophilus influenzae were first reported in the United States in 1974 and were at first limited to a few localities.[1-4] In subsequent years, clinical isolates resistant to ampicillin have been reported throughout the country and have necessitated changes in the recommendation of initial therapy of systemic hemophilus infection.[5] Despite this trend, cases of ampicillin-resistant hemophilus have been infrequently observed in California. In 1975 Overturf and his co-workers reported on their experience with antimicrobial susceptibility of Hemophilus influenzae at the Los Angeles County Hospital.[6] These investigators could detect no significant change in susceptibility to ampicillin during the previous decade. However, in an addendum to their paper, they noted their first highly resistant isolate which was obtained from a child with

From the Department of Pediatrics, Valley Medical Center and University of California, San Francisco, Medical Education Program, Fresno.
Submitted July 18, 1977.
Reprint requests to: Dan M. Granoff, MD, Dept. of Pediatrics, Valley Medical Center of Fresno, 445 South Cedar Avenue, Fresno, CA 93702.

ABBREVIATIONS USED IN TEXT
CIE = countercurrent immunoelectrophoresis
MBC = minimal bactericidal concentration
MIC = minimal inhibitory concentration

H. influenzae meningitis treated in Pasadena, California. Jacobsen and co-workers subsequently summarized data from 58 resistant isolates submitted to the Center for Disease Control through May 1975.[7] Only two of these were from California.

The purposes of the present report are to describe the emergence of ampicillin-resistant Hemophilus influenzae in Fresno County, California, and to confirm the usefulness of testing for β lactamase as an adjunct to routine antimicrobial susceptibility testing. The data to be reported are representative of the pathogenic strains isolated in this community and indicate that ampicillin-resistance has become a significant problem in the Central Valley of California and probably the entire state.

Materials and Methods

Fresno County has a population of approximately 450,000 and covers 6,000 square miles. The county is located in the Central Valley of California and surrounds the city of Fresno (population 165,000). A program of surveillance for ampicillin-resistant H. influenzae was begun at Valley Medical Center in September 1975. With the identification of the first resistant isolate in June 1976, this program was intensified by combining the clinical resources of Valley Medical Center and Valley Children's Hospital, the two hospitals in Fresno that provide nearly all acute pediatric inpatient care for the county and sparsely populated surrounding areas.

Isolates of Hemophilus influenzae obtained from blood, cerebrospinal fluid or joint aspirates were systematically referred from the clinical laboratories of the two hospitals to the Infectious Disease Research Laboratory. When multiple isolates were received from a single patient, the results from one of the isolates, usually blood, are reported. In addition to receiving isolates from invasive infection, selected type B strains obtained from other sites, primarily respiratory secretions, were also sent to our laboratory. Some were selected randomly, and others were referred because there was a question of ampicillin-resistance on the basis of the disc agar diffusion test. Strains cultured from mucous membrane sites were studied only if the organism was the predominant isolate in the specimen.

After isolation on chocolate agar, H. influenzae was identified by methods previously described,[8] except that antigenic typing was done by slide agglutination instead of the Quellung reaction. Antimicrobial susceptibility of Hemophilus influenzae was done by the clinical laboratory using Kirby-Bauer disc agar diffusion.[9] However, chocolatized sheep blood agar was used instead of supplemented clear media.

Upon receipt of hemophilus isolates in the Infectious Disease Research Laboratory, β lactamase production was measured using the method of Escamilla.[10] Specific antigenic typing of the positive isolates was confirmed by slide agglutination, or countercurrent immunoelectrophoresis (CIE)[11] in the presence of antisera types a-f (Hyland Laboratories, Costa Mesa, California).

Antimicrobial susceptibility was studied by broth dilution techniques for ten of the 11 isolates identified as positive for β lactamase, and for 30 β lactamase-negative isolates, including those initially recorded by the clinical laboratory as possibly resistant to ampicillin. We used brain-heart infusion broth supplemented by 5 percent Fildes extract (Difco Laboratories) and an innoculum of bacteria in log phase growth carefully diluted to a final concentration of 10^4 colony forming units per ml. The minimal inhibitory concentration (MIC) was recorded after 24 hours incubation at 35°C.[12] The minimal bactericidal concentration (MBC) was obtained by subculturing 24-hour broth cultures onto chocolate agar and determining the concentration of ampicillin that resulted in 100 percent reduction of bacterial growth. A known ampicillin-sensitive strain, and an ampicillin-resistant Hemophilus influenzae type B strain (MIC, 62 μg per ml) obtained from the Center for Disease Control were tested in each assay.

Results

During the 12 months ending June 15, 1977, eight Hemophilus influenzae type B strains were isolated at the two hospitals and confirmed by our laboratory as β lactamase positive or resistant to ampicillin (Table 1). They represented 4.8 percent of all type B strains identified at the two institutions.

There were 48 patients with invasive hemophilus infections who had organisms identified in blood, cerebrospinal fluid or joint aspirates. Of

TABLE 1.—*Hemophilus influenzae Type B Isolated at Two Hospitals in Fresno County, California (June 15, 1976—June 14, 1977)*

Specimen	Total Number of Isolates	β Lactamase Number Tested	β Lactamase Number Positive	β Lactamase Percent of Total
Blood, cerebrospinal fluid or joint aspirate	48	42	2	(4.2)
Other	117	62	6	(5.1)
TOTAL	165	104	8	(4.8)

these, 42 were tested for β lactamase and 2 were positive. The six isolates not tested were from cultures obtained during the first six weeks of the study and were inadvertently not sent to our laboratory. One of these isolates was recorded as resistant to ampicillin.

In all, 117 patients had Hemophilus influenzae type B as the predominant organism in cultures of other sites, primarily respiratory secretions. A total of 62 isolates were assayed for β lactamase activity and 6 were positive. The remaining 55 isolates were not tested for β lactamase but were reported as sensitive to ampicillin by the clinical laboratory.

Three ampicillin-resistant, nontypable Hemophilus influenzae isolates were also identified during this period. However, nontypable Hemophilus influenzae were not systematically examined and for this reason we cannot estimate the incidence of ampicillin-resistance among these strains. It is of interest that two of the nontypable strains were from patients initially infected with ampicillin-sensitive organisms. One patient had chronic bronchitis and the original isolate was grown in nearly pure culture from sputum. The second patient was an infant with otitis media who had heavy Hemophilus influenzae grown from middle ear drainage. In both patients, the organisms were initially sensitive to ampicillin when tested by disc agar diffusion, *and were negative for β lactamase.* Treatment with ampicillin resulted in poor clinical responses, and repeat cultures 30 days later in the patient with bronchitis, and 10 days later in the patient with otitis media, showed ampicillin-resistant Hemophilus influenzae positive for β lactamase.

Further data on the three nontypable and eight type B ampicillin-resistant hemophilus are shown in Table 2. Ampicillin-resistant strains were detected in Fresno throughout the year but more than half of the isolates were observed during the most recent three months. Resistant Hemophilus organisms were isolated from patients of all ages (range: 1 month to 63 years). There were two adults in the group and one of the two had bacteremia caused by a confirmed, ampicillin-resistant organism. It is possible that there were other adults in Fresno County with resistant hemophilus infection during the 12 months because our surveillance was primarily directed at childhood infections.

Although we initially defined ampicillin-resistant Hemophilus influenzae as organisms with an MIC greater than 3 μg per ml, all ten of the β lactamase-positive isolates studied by tube dilution techniques had MIC's of 15 μg per ml or greater. The MBC's were one tube dilution higher in five of the isolates and two tubes higher in the remaining five of the group.

Thirty Hemophilus influenzae type B isolates negative for β lactamase production were selected

TABLE 2.—*β Lactamase-Producing Isolates of Hemophilus influenzae Identified at Two Hospitals in Fresno County, California (June 15, 1976—June 14, 1977)*

Patient	Date	Age of Patient	Source	Type	MIC μg/ml	MBC μg/ml
1. ...	6/15/76	2½ years	Tracheal aspirate	B	31	125
2. ...	7/19/76	13 months	Throat	B	62	125
3. ...	7/27/76	6 months	Cerebrospinal fluid	B	ND	ND
4. ...	9/29/76	6 years	Sputum	B	62	250
5. ...	11/17/76	11 months	Ear	B	31	125
6. ...	4/ 4/77	63 years	Blood	B	31	62
7. ...	4/13/77	5 months	Eye	NT	31	62
8. ...	4/19/77	1 month	Eye	B	15	62
9. ...	5/10/77	13 years	Sputum*	NT	15	31
10. ...	5/20/77	10 months	Ear*	NT	31	125
11. ...	6/13/77	56 years	Sputum	B	31	62

MBC = minimal bactericidal concentration
MIC = minimal inhibitory concentration
ND = not done
NT = nontypable

*Initial isolates were ampicillin-sensitive and negative for β lactamase.

for further study of ampicillin susceptibility by tube dilution techniques. Twelve had MIC's of less than 0.35 μg per ml, 16 had MIC's of 0.7 μg per ml and two isolates had MIC's of 1.5 μg of ampicillin per ml. No β lactamase-negative isolate was detected that was resistant to ampicillin.

Standardized Kirby-Bauer disc diffusion sensitivity testing as done by the clinical laboratory was a reasonable, but not invariably accurate, method for determining ampicillin-sensitive and resistant hemophilus isolates. False resistance was reported in nine isolates, or 5.8 percent of susceptible strains. False susceptibility was reported in one of the ampicillin-resistant isolates (zone size, 21 mm) and occurred in the adult with bacteremia who had four positive blood cultures. The initial report in this patient led to continuation of ampicillin therapy for four days, during which the patient's condition deteriorated.

All strains sensitive or resistant to ampicillin encountered during the 12 months were susceptible to chloramphenicol.

Discussion

Beginning in June 1976 ampicillin-resistant Hemophilus influenzae emerged as important pathogens in Fresno County, California. Resistant Hemophilus organisms accounted for two and possibly three cases of invasive disease. In addition, several days after the admission to hospital of the patient in our initial index case, Hemophilus influenzae meningitis developed in a close playmate of this patient during a trip to Kern County, California. The isolates from the playmate were repeatedly tested at the local hospital using established disc agar diffusion methods,[9] and were found to be resistant to ampicillin (zone size, 13 mm). This patient's isolates were not included in our results because the child was admitted to hospital outside of Fresno County. However, she is of particular interest because of the clustering of the two cases.

Disc agar diffusion sensitivity testing has been previously reported to be an accurate method for differentiating between ampicillin sensitive and resistant Hemophilus influenzae.[9,12] Chocolate agar, which was employed by the clinical laboratories during our study, was found to be less reliable for sensitivity testing of hemophilus than supplemented clear media such as Mueller Hinton. When grown on chocolate agar, resistant strains showed a gradation of growth around the ampicillin disc and the endpoint of the zone was more difficult to determine. It was also more difficult to see small amounts of growth in the inhibiting zone, the resistant colonies being more apparent on clear media. We experienced similar difficulties with our sensitivity cultures on chocolate agar and no longer employ this medium for sensitivity testing.

The observation that nearly all ampicillin-resistant Hemophilus influenzae produce β lactamase allows us to use this property as a method for detecting resistant organisms. A number of practical, rapid and accurate enzymatic assays have been described for detection of this enzyme,[10,13-15] and the use of one of these circumvents many of the technical difficulties encountered in traditional antimicrobial susceptibility testing of Hemophilus influenzae.[12] Our experience supports the previous recommendation that clinical laboratories routinely test for this enzyme as an adjunct to standard Kirby-Bauer disc sensitivity testing.[9,15]

Emergence of ampicillin-resistant, Hemophilus influenzae in patients receiving ampicillin therapy is rare and, to our knowledge, has not been previously reported in patients with otitis media or purulent bronchitis. However, the cases of two patients with Hemophilus influenzae type B meningitis have been described in which the original infections were caused by ampicillin-sensitive organisms, and in which relapses were associated with ampicillin-resistant, β lactamase positive strains.[16,17] It is possible that the *original* infections in these patients as well as in our patients were caused by a mixed population of resistant and sensitive Hemophilus influenzae, and that initial sensitivity testing and enzymatic assays failed to detect the small proportion of resistant organisms. A third patient with Hemophilus influenzae meningitis has been reported in whom the original cerebrospinal fluid culture showed a mixed population of ampicillin-resistant and sensitive organisms.[2]

Previous reports of ampicillin-resistant Hemophilus influenzae infection have described localized outbreaks caused by resistant organisms,[1-3] or have presented data from isolates studied at the Center for Disease Control,[7] or a large university hospital[18] where the frequency of resistant organisms may have been biased by patient referral patterns. Despite these differences, the incidence of ampicillin-resistance found in the present study corresponds closely to reports from other centers, and to data recently gathered at

the Center for Disease Control (Clyde Thornsberry, personal communication). However, it should be noted that we did not test for β lactamase in all of the hemophilus strains isolated by the clinical laboratories. For this reason the 4.8 percent incidence of ampicillin resistance reported for Fresno (Table 1) is a *minimal* figure, since some resistant organisms may have gone unrecognized. At present our data support the recommendation of the American Academy of Pediatrics that chloramphenicol be employed in the initial therapy of suspected systemic Hemophilus influenzae type B infections. Results of antimicrobial sensitivity testing *and* assays of β lactamase production should be utilized by clinicians in deciding whether or not to continue therapy with ampicillin or chloramphenicol.

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Blood Loss in the Colon

DR. CLOUSE: ". . . most of the blood losses from the colon, about 90 percent of them, are from diverticula and about 75 percent of the blood losses from diverticula are from the right side of the colon rather than the left. So the concept of doing a left colectomy blindly is, I think, probably not justified before angiography. A patient has to be losing probably 0.5 to 1.0 ml of blood a second for bleeding from the gastrointestinal tract to be shown easily by angiography."

—MELVIN E. CLOUSE, MD, *Boston,* citing a paper by William Joseph Casarella of Columbia-Presbyterian Medical Center, New York City.

Extracted from Audio-Digest Surgery, Vol. 23, No. 16, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Drasin H: Treatment of malignant pheochromocytoma.
West J Med 128:106-111, Feb 1978

Treatment of Malignant Pheochromocytoma

HARRY DRASIN, MD, *San Francisco*

Pheochromocytoma is a tumor derived from chromaffin tissue, which secretes catecholamines. Today, about 90 percent of patients with this tumor are cured by surgical procedures. In 8 to 15 percent of patients with this tumor there is unresectable, recurrent or metastatic disease, which causes significant morbidity and mortality. The natural history of metastatic disease includes long-term survivors; many, however, die early of disseminated disease. The most common site of metastatic lesions is the skeleton. Palliation for these lesions can often be achieved with the use of radiation therapy. Other sites are, in general, less responsive to radiation therapy. Chemotherapy has been used in combination with radiation therapy, but the results generally have been disappointing. Chemotherapy with doxorubicin hydrochloride and cyclophosphamide in combination with radiation therapy has provided good palliation for skeletal disease for about five months, when disease progression was again noted. Further information is needed concerning the optimal chemotherapeutic treatment of this unusual tumor.

PHEOCHROMOCYTOMA is a tumor derived from cells in adrenal medullary or paraganglion tissue, and is characterized most often by the secretion of catecholamines. An uncommon tumor, it is recognized by the associated hypertension. Metastatic disease is defined by the presence of chromaffin tissue in areas where none is usually found, such as liver, lymph nodes, bone marrow, lungs or bone. Metastasis is present in 8 percent to 15 percent of all patients with pheochromocytoma.[1-4]

Today, the primary lesion is curable in 90 percent of patients by surgical operation alone. In the 1940's and 1950's, morbidity and mortality were invariably caused by cardiovascular complications, not by aggressive tumor, because patients often did not survive long enough for clinically significant problems from metastatic disease to be manifested. Today, effective antiadrenergic agents have significantly improved the quantity and quality of life for patients with nonresectable

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Supported in part by ACS Grant CF 3922, from the American Cancer Society.

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Submitted June 13, 1977.

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TABLE 1.—*Distribution of Metastatic Lesions in 41 Cases of Malignant Pheochromocytoma**

Location	*26 autopsy cases*	*15 nonautopsy cases*	*Percent*
Skeleton	12	6	44
Liver	12	3	37
Lymph node	11	4	37
Lungs	9	2	27
Central nervous system	4	0	10
Pleurae	4	0	10
Kidneys	2	0	5
Pancreas	1	0	2
Omentum	1	0	2

*From Schönebeck J: Malignant pheochromocytoma. Scand J Urol Nephrol 3:64-68, 1969. Reproduced with permission of the author and publisher.

tumors. The effect of these agents on the growth of the tumor or on its ability to metastasize, has not been defined. The natural history, even of metastatic disease, may be quite prolonged, and stable disease may persist for many years.[5]

Schönebeck reported the distribution of metastatic lesions in 41 patients[6] (Table 1). The skeleton, involved in 44 percent of patients, was the most common site. The liver and lymph nodes followed, with 37 percent each; lungs were affected in 27 percent; central nervous system, 10 percent; pleura, 10 percent; kidney, 5 percent; pancreas, 2 percent, and omentum, 2 percent.

This review summarizes reports of the use of radiotherapy and chemotherapy in the treatment of this most unusual disease.

Radiation Therapy in Metastatic Pheochromocytoma

The use of radiation in the treatment of malignant pheochromocytoma dates back to 1929.[2] Radiation therapy was applied to the primary lesion (before good surgical and anesthetic techniques had been developed), as adjunctive treatment after surgical procedures, in the treatment of local recurrence and in the treatment of metastatic disease. Overall, the tumor is considered to be relatively radioresistant. The physiological basis for this is thought to be the fact that catecholamines tend to lower tissue oxygen tension, thereby protecting these cells from radiation-induced damage.[3,7] It is well known that hypoxic cells are much less susceptible than normal or hyperoxic cells to radiation-induced injury. Results of radiation therapy are shown in Table 2.

Inconclusive Results

Numerous studies have documented the absolute resistance, or only partial response, of the pheochromocytoma to therapy. Graham summarized the data to 1949 on the use of radiation to treat the primary tumor. Operative mortality at that time was 26 percent. He concluded that radiation was ineffective treatment for the primary tumor.[2]

Engelman reported that a 12-year-old girl who received postoperative radiation therapy after incomplete surgical removal of a pheochromocy-

TABLE 2.—*Results of Radiation Therapy in the Treatment of Metastatic Malignant Pheochromocytoma*

Reference		*Patients*	*Result*	*Comment*
Boreus[9]	1968	1	Ineffective	Blood pressure remained elevated
Chong[5]	1974	1	Effective	11-year survival noted
Cryer[12]	1976	1	Ineffective	Died of progressive disease
Engelman[8]	1964	4	Ineffective	Recurrence in previously irradiated field
Gifford[1]	1964	11	Effective	Only two patients received radiation therapy; 1 alive 12 years after bone metastases; the other alive after two years
Graham[2]	1951	..	Ineffective	Literature review up to 1949
Higgins[21]	1966	1	Effective	No evidence of disease at nine months
Holsti[3]	1964	1	Ineffective	Recurrent lung metastasis
		2	Effective	Moderate to good palliation
James[7]	1972	9	Effective	3,500-4,000 rads may be of definite value
Joseph[20]	1967	1	Effective	Pronounced symptomatic relief
Kvale[19]	1957	..	Effective	May prolong life after recurrence
Moloney[18]	1966	1	Effective	Contributed to one 15-year survival
Philipps[14]	1976	1	Not stated	Upper femora treated prophylactically
Robinson[10]	1964	1	Ineffective	
Scharf[11]	1973	1	Ineffective	
Scharf[17]	1970	1	Partly effective	Decrease in exophthalmos with orbital involvement
Schönebeck[6]	1969	1	Partly effective	Some pain relief; patient died with diffuse disease
Scott[4]	1976	4	Ineffective	
Soffer[13]	1961	..	Ineffective	Some symptom control possible

toma did well for two years.[8] He then noted metastatic liver disease, as well as tumor, in the previously irradiated field. He too concluded that radiation is not effective therapy for this neoplasm.

Boreus reported that in a patient given radiotherapy postoperatively there was no lowering of blood pressure following this treatment.[9] Holsti reported treatment of several patients, one of whom had recurrent lung metastatic lesions after treatment with 4,900 rads.[3] A second patient received postoperative radiation of 5,800 rads. Seven months later metastasis to the liver occurred and more radiation was delivered. Following that, the patient remained asymptomatic for three years. In a third patient the tumor was attached to the periaortic sympathetic plexus and it infiltrated both the aorta and the inferior vena cava. Because of its inoperability, the tumor was exposed to 5,000 rads. This resulted in decreased catecholamine secretion and a decrease in the size of the tumor, as shown by angiography. The patient was also free from the abdominal pain, nausea, vomiting, sweating and syncope that had previously been present.

Robinson treated a patient with metastatic pheochromocytoma involving the lower scapula and right clavicle, who suffered progressive deterioration despite radiation therapy to the bones.[10] In this patient metastasis to the liver subsequently developed. Scharf treated a patient in whom there was metastatic abdominal lymph node involvement.[11] After treatment with radiation therapy and chemotherapy (drug not specified), the patient died of progressive metastatic disease with widespread lesions.

Schönebeck treated a patient in whom there was metastasis to bone, lymph nodes, liver and lung, and recorded that radiation therapy was partially successful in relieving pain.[6] Scott described four patients managed with radiation therapy and chemotherapy (drug not specified), all of whom died with disseminated disease, one at nine months, another at 2 years, the third at 3 years and the fourth at 11 years, after diagnosis.[4]

A 57-year-old man with malignant metastatic paraganglioma involving the lymph nodes and skeleton received 2,000 rads to involved iliac bones, along with antiadrenergic agents, but did poorly, and died about four months later.[12] Soffer stated that radiotherapy is ineffective in the treatment of pheochromocytoma, although he noted partial control of symptoms in some cases.[13] Philipps treated a 10-year-old girl with bone metastasis to the upper femora with 4,000 rads in an attempt to prevent pathologic fractures. The overall treatment of this patient appeared ineffective, according to Philipps, and he supplied no further specific information concerning the irradiated bone.[14] Other authors, without mentioning specific clinical research, stated that irradiation is ineffective in the treatment of this tumor.[15,16]

Beneficial Results

Not all reports present such a bleak picture, however. James, reporting on the x-ray therapy aspects of pheochromocytomas, mentioned nine patients who were treated with radiation therapy.[7] Two in this group received radiation to primary unresectable lesions. In one there was no effect from the therapy, but the other was alive and well ten years later. Five of six patients who received less than 2,500 rads had no apparent response, and all died within seven months. One patient with metastasis to bone received 4,800 rads and survived 12 years. James concluded that intensive radiation therapy to a dose of 3,500 to 4,000 rads may be of definite value.

Scharf, in discussing a case of orbital metastasis, noted a decrease in disease-associated exophthalmos after radiation therapy and chemotherapy.[17] Diffuse metastatic disease appeared, however, and the patient died six months later. Moloney reported success in treating his patients in whom there was metastasis to bone with radiation therapy.[18] He stated that high dose radiation therapy definitely contributed to a 15-year survival in one patient. Kvale felt that radiation therapy may prolong the life of a patient after recurrence.[19] Several of his patients, however, did have progressive disease despite radiation therapy. Joseph reported a patient's dramatic relief of symptoms, including pronounced lowering of blood pressure, after treatment of clavicular metastasis with radiotherapy.[20] The disease recurred, and further symptomatic benefit resulted from additional radiation therapy and chemotherapy.

Higgins treated, with up to 4,000 rads, a patient with pheochromocytoma of the urinary bladder which involved periaortic and internal iliac nodes; there was no evidence of disease at nine months.[21] Gifford noted that one patient was alive 12 years after treatment for metastatic bone disease, and another was alive 2 years after radiation therapy.[1] He concluded that radiation therapy was effective in these patients.

Chong reported postoperative radiation therapy to a patient in whom nonresectable lesions were found at surgical operation.[5] Metastasis to bone developed four years later and remained stable for seven years.

At Mount Zion Hospital and Medical Center, we treated a 70-year-old man who had been admitted in May 1975 for evaluation of low back pain thought to be caused by degenerative disc disease. In the hospital, palpitations, sweating, dyspnea and transient blood pressure elevations up to 300/190 mm of mercury occurred. At surgical operation, a large left adrenal tumor was found. There was no gross evidence of dissemination at operation, but on pathologic examination evidence of local invasion was found.

In January 1976 severe back pain and vertebral collapse occurred, and the patient was treated with a T-6 to L-3 field, 3,700-rad total dose in 22 fractions over 37 days, with good local pain relief. In the following months, however, progressive back pain and metastasis to the lower dorsal vertebrae were discovered. During this admission, lower lumbar and sacral fields received 3,600 rads in 18 fractions over 25 days. Because of extensive progressive disease and a bone scan showing multiple diffuse sites of involvement, the patient was placed on systemic chemotherapy using cyclophosphamide and doxorubicin hydrochloride in combination with radiation therapy. Now, eight months following his last admission, he remains relatively free of pain and is ambulatory. The disease has progressed slowly, involving new areas of the skeleton, and the patient is receiving local radiation therapy for these metastatic lesions. He is still receiving chemotherapy and tolerating it well. It appears that this combined modality treatment may have slowed the progression of disease, but did not prevent it.

Discussion

There is no overall consensus on the value of radiation therapy in this disease. Often, careful follow-up and details of the original and subsequent treatment programs are not provided. It does appear that the use of radiation therapy to treat primary lesions is not indicated. Its use postoperatively as adjuvant therapy has not been helpful in preventing local recurrence or dissemination and it has, therefore, not been of proven value.

The treatment of bone and, perhaps, lymph node metastatic lesions, does appear to provide symptomatic relief, and radiation therapy should be used when needed for palliation. There are no data pertaining to treatment for liver or bone marrow involvement. Doses of approximately 4,000 rads seem to provide the best responses. In summary, radiation therapy may be of definite value in treating bone and lymph node disease, and is capable of providing excellent, often long-term, pain relief. Since metastatic lesions have been shown to secrete catecholamines[22] this therapy may delay adverse cardiovascular effects of these compounds as well.

Chemotherapy

The literature contains few reports of the use of chemotherapy in treating pheochromocytoma, (see Table 3). Moreover, chemotherapy has al-

TABLE 3.—*Results of Chemotherapy in the Treatment of Metastatic Pheochromocytoma*

Reference		*Drugs*	*Radiation Therapy Also*	*Effect*	*Comment*
Joseph[20]	1967	Cyclophosphamide	+	Effective	Pronounced symptomatic relief
Moloney[18]	1966	Cyclophosphamide	−	Ineffective	Patient died of progressive disease
		Nitrogen mustard	+	Ineffective	
		Thiotepa	+	Ineffective	
Philipps[14]	1976	Vincristine and cyclophosphamide	+	Ineffective	Patient died of pseudomonas infection
		Doxorubicin hydrochloride	−	Ineffective	
Rosenbaum*	1976	Doxorubicin hydrochloride and cyclophosphamide	+	Effective	Symptomatic relief
Scharf[11]	1973	Cyclophosphamide, methotrexate	+	Ineffective	.....
Scott[4]	1976	Unspecified	?	Possibly effective	9-month, 2-, 3-, and 11-year survival

*Mount Zion Hospital and Medical Center, San Francisco.

ways been used in combination with radiation therapy, making it difficult to evaluate specific drug effects. Scharf used methotrexate and cyclophosphamide in combination with radiation therapy to treat a patient with abdominal nodal disease, without apparent benefit; the patient died of disseminated metastatic disease.[11] Another patient was noted to have decreased exophthalmos after treatment for orbital metastasis with chemotherapy and radiation therapy.[17]

Joseph used radiations to treat a patient with a recurrent pheochromocytoma, with resultant pronounced symptomatic relief and a decrease in blood pressure.[20] He gave cyclophosphamide, 2,600 mg over 14 days, following it with a maintenance dose of 150 mg daily by mouth. Scott reports the treatment of four patients with metastatic pheochromocytoma, using chemotherapy and radiation therapy, and mentions survivals of nine months and 2, 3 and 11 years after diagnosis.[4] Moloney treated a patient with metastasis to bone with thiotepa, 210 mg given intramuscularly in seven weekly doses of 30 mg, and noted a result of decreased cervical pain.[18] Arm pain progressed, however, and the bone was irradiated with 2,000 rads, producing good relief. Metastasis to the lungs then developed, and 30 mg of nitrogen mustard was given intravenously without response. Cyclophosphamide was then tried, and decreased levels of urine catecholamines resulted, but the patient died four months later of progressive disease.

Phillips used vincristine, 1.5 mg per sq meter of body surface, and cyclophosphamide, 300 mg per sq meter, intravenously weekly for six weeks, then every other week for 24 weeks, and noted slow deterioration of the patient's condition. The patient then received two courses of doxorubicin hydrochloride, but died subsequently of Pseudomonas pneumonia and sepsis.[14]

At Mount Zion Hospital and Medical Center, we treated a patient (a case also discussed in the section on beneficial radiotherapy effects) who had progressive metastatic bone disease, with radiation therapy and doxorubicin hydrochloride and cyclophosphamide—doxorubicin hydrocholoride, 40 mg per sq meter of body surface on day 1, and cyclophosphamide, 200 mg per sq meter by mouth on days 4 to 6, the cycle being repeated every three to four weeks. This combination, in conjunction with radiation therapy, was effective in relieving significant back pain, and decreased the patient's narcotic requirements, for a period of five months. Despite this treatment, however, skeletal disease continued to progress, at a slower rate than before the treatment.

Discussion

No controlled study exists in the English language literature to guide therapy for this disease. Some of the best responses have occurred with alkylating agents used singly, and perhaps even more benefit resulted from using a combination of alkylating agent and doxorubicin hydrochloride. Definite suggestions for drug use await further data.

Conclusions

While patients with pheochromocytoma can usually be cured with surgical procedures, patients with metastatic disease present a difficult problem. Life can be prolonged by the use of antiadrenergic agents which counteract the cardiovascular effects of the tumor. Perhaps, as more patients are treated with these agents and their lives thereby prolonged, we will see more metastatic disease. Metastasis to liver, lung or bone does cause morbidity and mortality in itself.

These metastatic lesions are relatively radioresistant, but significant palliation of metastasis to bone is possible with radiation therapy. Chemotherapy has almost always been used with radiation therapy, and therefore its effects are difficult to define. The control of disseminated metastatic disease has not been accomplished by using radiation therapy or chemotherapy alone or in combination. Further studies are awaited to better define the use of new methods of radiotherapy and new drug combinations in the treatment of this unusual disease.

Addendum

Hamilton[23] recently has reported the failure of streptozocin to affect either the catecholamine excretion or the tumor growth in two patients.

Our patient died in August 1977. This was 27 months after diagnosis, and 19 months after symptomatic metastatic disease was noted.

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Complications of Diuretics

RECENTLY THERE have been several reports of an intriguing syndrome of interstitial nephritis, especially after the use of furosemide. . . . For some reason this has been reported primarily in patients who have some form of preexisting renal disease and usually membranous glomerulonephritis. The syndrome is fairly clear-cut in that the patients have a peripheral eosinophilia, pronounced oliguria and the other manifestations of some sort of an allergic disorder. Stopping the administration of diuretics has completely brought renal function back to what it was at the time the agents were first utilized. . . . We have seen a number of patients with membranous glomerulonephritis who are receiving furosemide, but we have not clearly witnessed this syndrome ourselves.

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Extracted from *Audio-Digest Internal Medicine*, Vol. 24, No. 10, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Hoff JT, Spetzler R, Winestock D: Head injury and early signs of tentorial herniation—A management dilemma. West J Med 128:112-116, Feb 1978

Head Injury and Early Signs of Tentorial Herniation

A Management Dilemma

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In 100 patients intracranial exploration was done soon after severe head injury when signs of transtentorial herniation were present. A third of patients had extracerebral hematomas shown on initial burr hole examination. An additional 18 percent had parenchymal clots of clinical significance disclosed only by angiography after burr hole exploration or at autopsy. Half the patients in whom exploration was done did not have intracranial hematomas of sufficient size to warrant an operative approach. Detailed neurological examinations soon after injury and the availability of more rapid diagnostic tools may improve the accuracy of early diagnosis and allow more specific prognostication in patients with severe head injury.

When physical signs of brain stem compromise are present in patients soon after severe head trauma, the injury may be primarily to the brain stem or secondarily from compression of the midbrain by supratentorial structures herniating through the tentorial notch.[1] In either circumstance, similar physical signs may be present—coma, pupillary abnormalities, and extensor rigidity or flaccidity of the extremities.[2-4] The correct diagnosis, from initial physical signs alone, may then be difficult.[5]

Patients with transtentorial herniation may have one or all of a variety of supratentorial lesions—epidural or subdural hematomas (or both), intracerebral clots and diffuse cerebral contusions with brain swelling. Most intracranial hematomas, when present, are extracerebral,[1,6-8] lending themselves to discovery by trephination, by angiography, by radionuclide scanning and by computed axial tomography (CT scanning).

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Submitted June 8, 1977.

This study was supported in part by the Trauma Center Program Project GM 18470 and NS 11539, Trauma Center Fellowship Grant NIGMO 7032 (Dr. Spetzler), grants of the National Institutes of Health, USPHS.

Dr. Hoff is recipient of Teacher-Investigator Award NS 11051 of the NIH, USPHS.

Presented in part at the Annual Meeting of American Association for Surgery of Trauma, Scottsdale, Arizona, September, 1975.

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Surgeons agree that optimal care of patients with head injuries is best provided when a specific diagnosis is available before operative treatment. However, to provide an accurate diagnosis by current radiographic techniques requires time. For example, cerebral angiography rarely can be accomplished in less than two hours;[9] CT scanning requires a comparable amount of time, although more rapid diagnosis by this technique may be possible in the future.

A physician may elect to observe and support the patient for an indefinite period, or use diagnostic tools available to him (such as angiography, CT scanning) before beginning treatment of a specific lesion. Alternatively, he may treat the patient immediately by all medical and surgical means including exploration, on the premise that time lost testing is better spent treating. In general, a poor prognosis for patients with brain stem signs soon after injury has provided an adequate rationale for each of these management approaches.[8,10,11]

On the assumption that tentorial herniation is an emergency which becomes more profound with time, we elected to explore patients with head injury who had signs of herniation upon admission or soon after. This approach, while not new, was designed to focus on obvious neurological signs, rather than upon a specific disease entity. Information gathered from this approach could be helpful in a physician's first moments of contact with an injured patient. To date similar data have not appeared in the literature. We sought to (1) establish the incidence of extracerebral hematomas in trauma victims who have early brain stem signs, (2) determine what percentage of patients might benefit from early operation and (3) based on these data, assess the effectiveness of traditional burr holes as a diagnostic and therapeutic technique.

Patients and Methods

From 1972 through 1974 we carried out exploration by multiple burr holes in 100 patients with severe head injury who had signs of brain stem compression immediately upon or soon after admission. Of the patients, 72 were male and 28 were female. The average age was 38 years (range, 2 to 88 years). Most injuries were the result of traffic accidents, falls or assault. The time from injury to hospital admission was usually less than a hour because of the rapid delivery and triage of patients seen on an emergency basis in the San Francisco area.

TABLE I.—*Physical Signs Before Operation in 100 Patients*

Signs	*Percent*
Stupor	4
Coma	96
Flaccid extremities	14
Extensor rigidity	51
Fixed pupil dilatation	84
Unilateral	47
Bilateral	37
Other major injury	30

During the same period (1972 through 1974) operations were carried out in 147 other patients with less severe head injuries, after angiography had identified specific intracranial hematomas. Clinical signs of herniation were not obvious in those 147 patients before the radiographic study; therefore they were excluded from this review.

Diagnosis

All 100 patients had severe depression of consciousness on admission to hospital. Physical signs during the interval from admission to operation (less than two hours) are listed in Table 1. The most common neurologic sign leading to urgent operation was profound disturbance of consciousness that failed to improve promptly. In all, 96 patients were unresponsive to all stimulation except pain before operation. Most (65 percent) showed either extensor rigidity or flaccidity of the extremities; the other 35 percent retained variable degrees of purposive, spontaneous movement of the arms and legs. In 84 patients there were pupillary signs of transtentorial herniation before operation. A unilateral dilated pupil which failed to respond to light was common (47 percent); 37 patients (37 percent) had bilateral fixed, dilated pupils. Therefore, the classical triad of physical signs indicating transtentorial herniation[2,4]—coma, extensor rigidity or flaccidity of the extremities, and fixed dilatation of one or both pupils—was common soon after injury.

In 57 patients skull radiographs were obtained before operation; in 37, a fracture was shown. Plain skull films showed no abnormalities in 20 patients; a pineal shift was present in three patients. In 43, skull films were not made before operation because neurological deterioration was precipitous during the initial evaluation, or physical signs of herniation were present on arrival at

TABLE 2.—*Autopsy Findings in 48 Patients*

Findings	*Percent*
Cortical hemorrhages	98
Cortical necrosis, lacerations	52
Intracranial hematoma	21
Extracerebral	10
Intracerebral	9
Cerebellar	2
Brain stem hemorrhages	62

the hospital. When skull films were obtained, cervical spine films were taken also; one patient had a cervical fracture (2 percent). Thirty patients had multiple injuries. In 19 an emergency operative procedure was required for abdominal, thoracic or extremity trauma.

Treatment

When initial resuscitation was complete all patients received dexamethasone intravenously (10 mg). Mannitol (500 ml, 20 percent) was begun intravenously in 91 patients before operation. Ventilation was assisted, if necessary, to maintain arterial carbon dioxide pressure between 25 and 35 mm of mercury.

Burr holes were made bilaterally at three sites: frontal, occipitoparietal and temporal. A clinically significant hematoma was encountered epidurally in four patients. In 30 patients acute subdural hematoma was noted. Swollen, contused cortex was evident, without an extracerebral mass, in the remaining 66 patients. If an extracerebral clot was evident through a burr hole, it was removed immediately by craniotomy. If no extracerebral hematoma was present, needle aspiration of the brain through the burr holes was not carried out.

When no hematoma could be found by burr holes, cerebral angiography was then done in 32 patients. The circulation of the carotid and one vertebral artery was studied by the transfemoral route. An intracerebral mass effect was apparent in 18 of the patients (56.2 percent) who were analyzed in this manner. Seventeen had a supratentorial parenchymal mass; one had a cerebellar hematoma. Of these deep masses not shown by burr holes, but identified by angiography, nine were judged sufficiently large and localized to require operative removal by craniotomy.

Postoperative support included dexamethasone administration, intermittent mannitol infusion, temperature control and ventilatory support.

TABLE 3.—*Physical Signs Before Operation in Survivors and Nonsurvivors, 100 patients*

Signs	*Survivors (47) Percent**	*Nonsurvivors (53) Percent**
Stupor	6	2
Coma	94	98
Flaccid extremities	9	19
Extensor rigidity	49	53
Fixed pupil dilatation	70	96
Unilateral	57	38
Bilateral	13	59
Other major injury	28	32

*Percent of patients in each group.

Results

Survival

Of the 100 patients, 53 died. The autopsy findings in 48 are shown in Table 2. Primary parenchymal injury was severe, occurring in both the cerebral hemispheres and the brain stem. There were five cases of significant (greater than 50 cc) extracerebral hematomas, four of intracerebral clots and one of cerebellar hematoma. Nine of the ten patients with intracranial hematomas shown at autopsy *had not had angiography carried out* at any time during their hospital course.

Of the 47 patients who survived, a significant intracranial hematoma was removed after injury in 22. Included in these 22 survivors are four (of a total of nine) who survived removal of an intracranial hematoma shown by angiography after burr hole exploration had proved to be nondiagnostic. In the remaining 25 survivors operation for removal of an intracranial clot was not required.

Comparison of Survivors and Nonsurvivors

Physical signs before operation did not differ substantially between patients who survived and those who died (see Table 3). Flaccid extremities were more common in those who died (19 percent) than in those who lived (9 percent). Fixed pupillary dilatation, particularly when bilateral, suggested a poor outcome. Not surprisingly, patients who died were usually older than those who survived. But none of the physical signs we elicited consistently predicted the ultimate result.

When the three signs of transtentorial herniation were present before operation, a good result was unlikely. Of the 53 patients who died, 34 (64 percent) had classical herniation before operation, while such signs were apparent in only 15 of the 47 who survived (32 percent). Of in-

TABLE 4.—*Physical Signs Before Operation and Quality of Survival, 100 Patients*

Signs	Functional Recovery: Good (22) Percent*	Functional Recovery: Poor (25) Percent*	Died (53) Percent*
Stupor	9	4	2
Coma	91	96	98
Flaccid extremities	5	12	19
Extensor rigidity	36	60	53
Fixed pupil dilatation	64	76	97
Unilateral	55	60	38
Bilateral	9	16	59
Other major injury	36	20	32
Average age	28	29	38

*Percent of patients in each group.

terest was the finding that four patients who survived and then recovered fully had a complete triad of herniation signs before operation.[12] Two who became functional survivors had bilateral pupillary dilatation before burr hole exploration.

Quality of Survival

The quality of survival six months after injury ranged from complete functional recovery to persistent vegetative state.[13] A total of 22 patients were either independent or minimally dependent (good), while 25 were dependent or vegetative (poor) six months or longer after injury (Table 4). The actual presence or absence of a traumatic intracranial hematoma had little effect on the quality of life of patients who survived in our series.

Discussion

Patients included in this review had in common severe, traumatic brain injury and evidence of early brain stem compromise. Some had epidural hematomas, some subdural hematomas, some intracerebral clots and others diffuse injury without localized masses. The prognosis for each injury might have been different had the pathological entity (for example, epidural hematoma) itself been considered and the clinical state excluded.[7,9,14,15] But considering *clinical signs* as determinants of outcome, all patients were neurologically moribund at the time of exploration, suggesting that the prognosis would be poor regardless of the specific intracranial injury.

We proceeded to exploration early, assuming that both the correct diagnosis could be established and treatment rendered if an extracerebral mass causing transtentorial herniation was present. We further assumed that exploration, if findings were negative, would do no harm, provided standard supportive treatment was given simultaneously. When exploratory burr holes failed to reveal an extracerebral clot, many patients then underwent cerebral angiography to identify "missed" intracranial hematomas requiring removal. When a missed hematoma of clinical significance was found by angiography (nine patients), it was removed during a second operation.

In 34 patients there were extracerebral hematomas of clinical significance diagnosed by burr holes. All were evacuated by craniotomy. In the remaining 66 patients findings on exploratory burr holes were negative. Therefore, only in a third of our patients, most of whom had signs of transtentorial herniation within two hours of injury, were there extracerebral clots that were removed as early as possible.

Burr holes had given negative findings in 18 patients (18 percent) in whom an intracerebral mass was identified angiographically. The mass was sufficiently large in nine of them to warrant removal by craniotomy. Angiography showed one extracerebral mass, a parietal epidural hematoma, which had been missed by previous exploratory burr holes.

Of the 18 patients with negative burr hole findings in whom postoperative angiography was not done, 16 died from the brain injury; of these, a clinically significant intracerebral hematoma was found at autopsy in nine. Therefore, a total of 18 of the 100 patients reviewed had significant deep clots that were missed on burr hole exploration, and were or would have been recognized by angiography.

Nearly half (48 percent) of our patients in whom exploration was done did not have a mass sufficiently large to benefit from its removal. Thus nonoperative, supportive care was initially and subsequently the only therapeutic alternative.

It has been reported that patients who experience transtentorial herniation after head injury rarely survive, and that a good functional recovery is even less likely.[8,10,11] The results of our study confirm that prediction. Only four patients (8 percent) of the 49 with classical herniation before exploration recovered fully. Of the patients who died, 64 percent had a complete triad of herniation signs before operation, while 32 percent of those who survived had classical transtentorial herniation preoperatively. Therefore, while herniation suggested a poor outcome despite aggres-

sive management, it did not necessarily foretell it. Previous reports have verified that complete recovery may occur with proper therapy even though herniation may already have occurred.[9,12,16]

Survival from severe head injury is not only of medical interest, but also of socioeconomic importance. Recent reports have focused on this problem,[10,13] stressing the need for early clinical criteria that may predict outcome. Our study suggests that prognosis from very early signs may not be sufficiently accurate, using the simple bedside examinations reviewed in this study. For example, four of our 49 patients with classical signs of herniation from brain injury not only survived, but eventually recovered completely. The coma scale recently advocated by Teasdale and Jennett[17] and the more detailed clinical assessment used by Overgaard and co-workers[10] may afford more accurate prognostication at the crucial early stage of management.

Whether or not surgeons should still resort to exploratory burr holes remains an unanswered question. Occasional extracerebral clots and a substantial number (18 percent) of deep clots will be overlooked if burr holes are the first and last diagnostic procedure used. Fundamental to the problem is our inability to diagnose with certainty the most important of a host of intracranial lesions in trauma victims. Similarly, we do not know when signs of mid-brain compression are reversible and when they are not. And finally, we cannot yet accurately diagnose within the first few hours after injury those patients whose immediate, primary and permanent injury is to the brain stem itself.[18] Further development of visual, auditory and somatosensory evoked potentials may improve early accuracy.[19]

While our approach to the problem of severe head injury failed to differentiate with certainty patients who would recover from those who would not, it did yield practical information useful to surgeons who must consider early management alternatives in moribund trauma victims. When the physician is confronted with a patient who shows signs of tentorial herniation soon after head injury, immediate exploration via burr holes can probably help in about a third of the cases. Preoperative angiography or computerized scanning can identify a mass of clinical significance in half of the patients if the diagnostic delay imposed by the procedure can be tolerated, and almost all of the remaining patients will benefit only by aggressive, nonoperative, supportive care.

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Refer to: Gitnick GL: Viral hepatitis (Medical Progress). West J Med 128:117-126, Feb 1978

Viral Hepatitis

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Viral hepatitis may be classified into three or more forms including type A hepatitis, type B hepatitis, and a group denoted as non-A non-B hepatitis which may represent viral hepatitis of one or more causes. The differentiation of these forms of hepatitis is primarily serologic. The development of antibody to hepatitis A virus can be detected by radioimmunoassay as well as by other test systems. The serologic diagnosis of type B hepatitis rests on the detection of hepatitis B surface antigen or on the development of antibody to hepatitis B core antigen or hepatitis B surface antigen. The serologic diagnosis of non-A non-B hepatitis is a diagnosis of exclusion for assay systems for this form of disease are not yet available.

A prototype hepatitis B vaccine has been prepared and is currently undergoing clinical trials. Gamma globulin is now available that contains high titered antibody against hepatitis B virus. Normal immune globulin contains high titers directed against hepatitis A virus. Therefore, for documented exposure, effective prophylaxis is available for both of these forms of acute liver disease. The past decade has resulted in rapid advances in our understanding of the pathogenesis of acute hepatitis and its extrahepatic manifestations. However, it is clear that specific treatment for acute hepatitis and the accurate description of the etiologic agents of non-A non-B hepatitis require exploration.

THE MODERN serodiagnosis of hepatitis and the recent knowledge of its prophylaxis and management stem from an analysis of the blood of an Australian aborigine living distant from civilization. In the early 1960's Dr. Baruch Blumberg, a geneticist primarily interested in serum lipoproteins, discovered that multiply transfused patients frequently make antibodies directed against lipoprotein determinants.[1] In 1963, pursuing this observation, he tested the sera of multiply transfused patients with hemophilia and found that one reacted with the sera of an Australian aborigine. This serum specimen could also produce a pre-

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cipitin reaction with the sera of another patient with hemophilia.[2,3] Further characterization of the antigen showed that it differed from lipoproteins in that it stained only faintly with a lipid stain, but reacted well with a protein stain.[4] Since the antigen was found in the sera of an Australian aborigine, it was given the provisional name "Australia antigen."

Later, the antigen was frequently identified in the sera of patients with hepatitis. By 1970 the relationship of this new antigen-antibody system with viral hepatitis was well established.[5-7] It was also learned that the antigen-antibody system was associated not only with "serum" hepatitis but also with "infectious" hepatitis. Subsequent work resolved these apparent discrepancies and showed that both forms of hepatitis could be transmitted by the fecal-oral route, as well as by blood products.[8-10]

The name hepatitis associated antigen (HAA) was used for a short time and then was replaced with the name hepatitis B antigen (HBAg). Most recently, the terminology hepatitis B surface antigen (HB_sAg) and antibody to hepatitis B surface antigen (anti-HB_s) have been used. The availability of highly sensitive assay systems for HB_sAg and its antibody have allowed physicians to accurately diagnose this form of viral hepatitis while excluding drug induced and toxic liver disease, to identify exposures requiring prophylaxis and to implicate patients and personnel at risk after hepatitis transmission.

Our knowledge of hepatitis has followed a complex course over the past decade. The path has led to the first description of the morphology of hepatitis B virus and in time, the antigenic properties of the virus and the presence of a deoxyribonucleic acid (DNA) core were revealed.[11] Most recently, the "e" antigen has come into prominence.[12,13] Currently, three antigens are associated with the hepatitis B virus particle. These include (1) the surface antigen (previously called Australia antigen), (2) presumptively, the "e" antigen and (3) the core antigen which is the central component of the virus particle containing viral DNA.

The ability to detect the presence of these viral antigens has allowed physicians to assess the pathogenesis of associated conditions such as periarteritis,[14,15] glomerulonephritis[16,17] and arthritis;[18] as well as the chronic sequelae of acute hepatitis,[19] such as chronic persistent hepatitis, chronic active hepatitis,[20,21] postnecrotic cirrhosis and hepatocellular carcinoma. Recently, studies of short incubation endemic hepatitis have shown the presence of 27-nanometer viral particles which have been associated with hepatitis A. A sensitive radioimmunoassay for detection of hepatitis A antigen and antibody has been developed and new epidemiologic studies have given insight into the pathogenesis of this form of viral disease.

TABLE 1.—*Current Hepatitis B Terminology*

Antigen Name	*Standard Abbreviation or Term*
Hepatitis B virus	Dane particle
Hepatitis B surface antigen	HB_sAg
Hepatitis B core antigen	HB_cAg
"e" antigen	e Ag
Antibody to hepatitis B surface antigen	Anti-HB_s
Antibody to hepatitis B core antigen	Anti-HB_c
Antibody to "e" antigen	Anti-e

Current Terminology

Rapid changes in our concepts of hepatitis, and its chronic sequelae, pathogenesis and prevention have necessitated terminology to remain in a dynamic state of change. As our understanding of the antigens of hepatitis B expanded, new terms were developed leading to the use of new abbreviations. This report describes the terminology recommended by the International Association for the Study of Liver Diseases and adopted by most authoritative bodies in the United States.

Table 1 illustrates our current hepatitis B terminology and its relationship to the structure of hepatitis B virus. The whole virus particle is often called the Dane particle because of the original description by Dr. Dane. The surface of the virus is composed of hundreds of units. Each unit represents a single surface antigen which initially was called Australia antigen, and subsequently, hepatitis associated antigen, hepatitis B antigen; most recently it has been called hepatitis B surface antigen, as has been noted. Thus, each virus is associated with hundreds of hepatitis B surface antigens.

Also thought to be either on the surface of the hepatitis B virus particle or adjacent to the core is the "e" antigen (e Ag). This recently described antigen is separate and distinct from HB_sAg and is immunologically unrelated.

The central component of the hepatitis B virus is referred to as the core. The core contains DNA which could represent the infectious moiety of

the hepatitis B virus. The central core is known as hepatitis B core antigen (HB_cAg). DNA polymerase is found associated with the HB_cAg, and could be the basis of viral replication. The importance of this enzyme in the life cycle of the virus has not been established.

Each of the antigens of hepatitis B is associated with appropriate antibodies all of which develop during the normal course of resolving hepatitis. Thus, the antibody to HB_sAg is called anti-HB_s, the antibody to e Ag is called anti-e, and that to HB_cAg is called anti-HB_c. Table 1 lists these antigens, antibodies and the appropriate abbreviations.

The serologic diagnosis of hepatitis A currently rests on showing the development of antibody to hepatitis A virus as acute hepatitis progresses. The absence of such antibody before development of disease and the subsequent development of antibody or a four-fold or greater increase in titer confirms the diagnosis of hepatitis A. The abbreviation for hepatitis A antibody is anti-HA.

Subtypes of Hepatitis B Surface Antigen

HB_sAg particles have surfaces with multiple antigenic sites. In two dimensional double immunodiffusion assays, certain combinations of hepatitis B surface antigen and antibody reflect this antigenic complexity by the production of "spurs" in precipitin tests.[22] Analysis of these reactions has resulted in the differentiation of six antigenic determinants. Common to all antigenic groups is determinant "a." Subtypes of the "a" specificity include "d," "x" and "y." Subtypes of the "d" specificity are "w" and "r." Of the antigenic subspecificities outlined, the determinant "x" is present in most human HB_sAg positive sera. In contrast, determinants "d" and "y" are mutually exclusive and are not found together in the same sera. Therefore, HB_sAg positive sera possessing the group specificity "a" has been divided into three antigenic sets "d," "y" and "a" depending respectively on their possession of small "d" or "y" or neither of these determinants. It has been postulated that "d" and "y" reflect two different genotypes of the hepatitis virus which have been subtyped D or Y or may be described by their characteristic antigens as "a," "d" or "d positive" or "ay" or "y positive." Several studies indicate a greater prevalence of type "d" among asymptomatic chronic carriers of HBsAg and a prevalence of type "y" in acute hepatitis among drug users.

Clinical Applications of HBsAg Testing

Screening

The detection of HB_sAg among certain high-risk groups and the subsequent recognition of acute and chronic liver disease in these persons have led to a clear need for routine screening of specific populations for the presence of HB_sAg.

- *Dialysis Units.* Patients undergoing chronic hemodialysis and staff members working in dialysis units are at risk of acute and chronic hepatitis developing as well as becoming chronic carriers of HB_sAg. The patients, if hepatitis develops, are prone to low grade chronic liver disease. In these patients either chronic persistent or chronic active hepatitis may develop.
- *Oncology Units.* Patients and staff in oncology units have been found to be especially prone to hepatitis. In patients with lymphoproliferative disorders severe hepatitis develops and they are thought to be highly infectious. Chronic liver disease may develop in such patients with greater frequency than in patients without malignancies. This places personnel working in oncology units at risk; and accordingly, it has been recommended that patients and personnel in such units be routinely screened monthly for HB_sAg and for development of anti-HB_s. Antibody screening would identify those personnel who may have some level of immunity to hepatitis B antigenemia. Patients with solid tumors, such as carcinoma of the breast, may be at lesser risk for the development of chronic hepatitis. When they are exposed, hepatitis, which is usually associated with jaundice, frequently develops.
- *Other Hospital Areas.* Although most HB_sAg carriers probably are not infectious or, if infectious, are able to transmit at a very low level, occasional carriers are highly infectious. Since definitive information is not currently available regarding the infectivity of chronic carriers, a subcommittee appointed by the National Academy of Science has recommended that chronic carriers in paramedical and medical fields be advised not to alter their occupations or their procedures until more information regarding infectivity becomes available; or until the person has been shown to be an infectious carrier. Since most persons with antibody to hepatitis B surface antigen enjoy some level of protection from HB_sAg, it may be practical to screen hospital personnel for the presence of antibody and to assign those with

preexistent antibody levels to those units and areas in which hepatitis exposure is most likely.

The surgeon and surgical team may be frequently exposed to patients who are chronic HB_sAg carriers or who have occult liver disease. Presurgical screening of patients for the presence of HB_sAg may identify those patients who pose a risk to the surgical team or who have occult liver disease.

Differential Diagnosis of Acute Liver Disease

When confronted with a patient with symptoms of hepatitis, including anorexia, fatigue, arthralgias with or without jaundice, and elevated transaminase values, a physician is frequently confronted with a difficult differential diagnosis. Although it is clear that the patient is likely to have some form of hepatitis, it is important that the type of hepatitis be established both for prognostic and therapeutic implications. The usual clinical features of viral hepatitis are indistinguishable from those of a drug-induced hepatitis, toxic hepatitis or alcoholic hepatitis. Furthermore, even in patients not taking drugs, exposed to toxins or drinking alcohol, the type of viral hepatitis in the absence of serologic differentiation is usually unclear. In order to facilitate the characterization of acute and chronic liver disease, HB_sAg and anti-HB_s may be included in liver panels.

Three forms of acute viral hepatitis are commonly recognized. These are hepatitis A, B and a postulated type "C."

- *Hepatitis A.* Hepatitis A is usually characterized by a short incubation period of two to six weeks, mild prodromata and a relatively mild clinical illness. This disease is generally transmitted by contaminated food or water, but has been shown to be transmitted by systemic inoculation. This form of hepatitis was previously called "infectious hepatitis." A sensitive radioimmunoassay for the detection of hepatitis A antibody and for determination of the presence of hepatitis A antigen has been developed but is not yet commercially available. These serologic techniques may provide precise documentation of this form of acute liver disease.
- *Hepatitis B.* Previously, hepatitis B was usually associated with a long incubation period from six weeks to six months. Recently, incubation periods as short as two weeks have been documented after hepatitis B exposure. The illness may be mild or asymptomatic but, if symptomatic, symptoms may be especially severe. Prodromata may include arthralgias, arthritis, rash, fever leading to anorexia, fatigue and pruritus, with or without jaundice. This disease is generally transmitted by blood products or contaminated needles but is also found among people not exposed to blood or needles. It has been shown that hepatitis B may be transmitted albeit with difficulty by the fecal-oral route.

This form of hepatitis has been called "serum hepatitis" but the term is a misnomer since it is now well known that hepatitis B may be transmitted by other routes. Many body fluids besides blood have been shown to contain HB_sAg; these include urine,[22] saliva,[23] bile,[24] feces,[25] sneeze droplets,[26] semen,[27] vaginal secretions,[28] breast milk[29] and tears.[30] Venereal transmission of hepatitis B has also been documented.[31] There is a high incidence of HB_sAg and anti-HB_s in prostitutes and in male homosexuals.[31,32] Although family contacts of HB_sAg carriers are at risk for development of hepatitis, the risk appears especially high in the sexual partner.[31] HB_sAg may be transmitted transplacentally from an HB_sAg positive mother to her infant.[33,34] Other unusual modes for transmission of hepatitis B are indicated by a study showing HB_sAg in shellfish taken from contaminated waters and in infected clams.[35] HB_sAg has been found to persist in mosquitoes[36] after digestion of a blood meal and in bed bugs.

A highly sensitive radioimmunoassay for the detection of HB_sAg and its antibody now enables physicians to precisely document the presence of hepatitis B.[37,38] The antigen usually can be detected in serum before the onset of symptoms and before elevation in serum transaminase levels. The antibody frequently will develop at the height of symptomatology and the peak of transaminase levels. Therefore, serologic determination of the antigen may be made during the prodromata as well as during the acute phase of hepatitis. In those patients in whom a demonstrable antigen does not develop, seroconversions can be shown by the development of antibody to hepatitis B surface antigen at the peak or shortly after the peak of symptoms and biochemical abnormalities.

Recent data have shown that many cases of type B hepatitis will not be associated with demonstrable surface antigen using current assay techniques but the presence of an antibody seroconversion can be shown.[39] The development of anti-HB_s, therefore, specifically identifies acute hepatocellular disease as type B hepatitis. A recent study shows that most type B hepatitis, following

blood transfusions, is HB_sAg negative but will be associated with the development of anti-HB_s. In the case of acute hepatitis, the antibody develops late in the course of the disease or in the convalescent period.

The differential diagnosis of acute hepatitis includes drug-induced liver disease, alcoholic liver disease, toxic liver disease, hepatitis type A, hepatitis type B or the postulated "type C" hepatitis.[40] If the surface antigen assay is negative, the physician may find himself feeling safest in advising the patient to stop a necessary drug because of its possible contribution to the development of acute hepatitis; or may advise against the use of alcohol, even though it is uncertain as to whether alcohol is the cause of acute liver disease. The development of specific antibody to hepatitis B surface antigen or to the core antigen pinpoints the diagnosis and allows the physician to properly advise his patient. It may prevent the discontinuation of necessary drugs or the inappropriate implication of toxic or environmental materials. Therefore, the anti-HB_s and anti-HB_c assays provide a valuable tool in the modern diagnosis of acute hepatocellular disease.

The presence of "e" antigen suggests a high degree of infectivity. Many hepatitis B patients are transiently "e" antigen positive early in the course of their disease. The persistence of "e" antigen carries a guarded prognosis and suggests an increased risk for the development of chronic disease.

• *Non-A Non-B Hepatitis.* A large number of hepatitis cases are serologically and epidemiologically unrelated to hepatitis A or hepatitis B. These cases have been classified as non-A non-B hepatitis or as hepatitis "C." This may represent a single kind of hepatitis or several forms of hepatitis of differing viral causes. Non-A non-B hepatitis accounts for the vast majority of posttransfusion hepatitis now seen in the United States and for a significant proportion of endemic hepatitis seen in most communities. Incubation periods ranging from two weeks to six months have been documented, and while many patients lack significant symptomatology, others may present with anorexia, nausea, vomiting, fatigue and jaundice. Serologic assays for the determination of this form of hepatitis are not available; however, the absence of antigen or antibody related to hepatitis A or hepatitis B may be sufficient to classify patients into the non-A non-B category (Table 2).

Chronic HBsAg Carriers

Chronic carriers of HB_sAg may be free of liver disease; or may have one of the aforementioned chronic or acute liver diseases.[41-44] Usually, after four or more months of documented HB_sAg positivity, a person may be classified as a chronic HB_sAg carrier. Those factors leading to the carrier state are poorly understood. In one group of 26 infants exposed to HB_sAg *in utero* or during birth, 10 were found to be chronic carriers with protracted subclinical hepatitis. There is an unusually high frequency of HB_sAg carriers in patients in institutions such as those with Down syndrome. Chronic hemodialysis patients and patients in oncology units frequently become carriers, as do patients with lepromatous leprosy and patients with leukemia and compromised immune mechanisms. In some parts of the world, especially in the Philippines, New Guinea and Sardinia, a genetic predisposition to the carrier state has been documented as a simple autosomal recessive. It has been estimated that in the United States there are at least one million chronic HB_sAg carriers.

Outbreaks of hepatitis B have been traced to an HB_sAg positive dentist, oral surgeon and general practitioner.[45] In contrast, studies of contacts of HB_sAg positive personnel have shown no increased risk among their contacts as compared with a control population.[46]

Many chronic HB_sAg carriers, especially those in whom liver tests give abnormal findings, are found to have significant liver disease when a liver biopsy is done. The identification of a chronic HB_sAg carrier, with or without chronic liver disease, may raise some difficult social, ethical, legal

TABLE 2.—*Clinical Differentiation of Acute Hepatitis*

Feature	*Type A*	*Type B*	*Non-A Non-B*
Incubation Period	2 to 6 weeks or longer	6 to 24 weeks or less	6 to 24 weeks or less
Onset	Acute; mild prodromata	Insidious; often arthritis, rash, fever and severe fatigue	Insidious; mild prodromata
Transmission	Fecal-oral	Usually parenteral, may be nonparenteral	Usually parenteral, may be nonparenteral

and psychologic problems. Contact with HB_sAg positive blood, urine or feces represents a possible mode of hepatitis transmission to susceptible persons. However, it has not been established whether or not these body fluids are indeed infectious if obtained from chronic carriers without liver disease, and the absence of definitive data regarding infectivity makes it difficult to adopt strict recommendations.

At UCLA we have formed a carrier club. It became apparent to us that carriers represent a unique part of the population. They are healthy and usually are detected by voluntary blood donations. They accordingly represent an unusual segment of society: the willing volunteer. They are very concerned about the finding of antigen in their blood and are grateful when tests show the absence of acute or chronic liver disease. Nevertheless, the risk of liver disease to themselves in the future is an open question, and the risk that they represent to their contacts and family is reminiscent of that of social pariahs or lepers in earlier periods. In our ignorance, we neither want to suggest that such people be executed or placed on distant islands or in isolated camps, nor are we anxious to suggest that they become food handlers or blood bank technicians. By virtue of the club we have found a means of educating asymptomatic antigen carriers of the current state of ignorance or knowledge regarding the problem. We have advised them not to donate blood and to avoid sharing razors, toothbrushes and cigarettes. To deprive an antigen carrier of his occupation, whether he be a dentist, oral surgeon, general surgeon, nurse or chef, seems inappropriate in the absence of adequate epidemiologic data regarding individual infectivity.

Hepatitis Prevention and Control

In order to limit the spread of hepatitis, it has been emphasized that efforts must be directed at minimizing exposure to sources of infection. Personal and environmental hygiene must be maintained and disease surveillance, physician education and public education fostered. In May of 1976, a joint statement was issued by the Committee on Viral Hepatitis, Division of Medical Sciences, National Academy of Sciences-National Research Council and the Public Health Service Advisory Committee on Immunization Practices. The following recommendations, abstracted from the joint statement,[47] may offer guidance to those working with or associated with a hepatitis risk.

Disinfection

Unfortunately, most data on hepatitis inactivation were derived before current testing procedures were available. Definitive information regarding infectivity cannot be obtained in human volunteers for ethical reasons and animal models for hepatitis B are expensive and in short supply. Therefore, the data regarding infectivity are limited. The following methods for sterilization have been recommended either because of proven effectiveness or because of ability to destroy immunologic reactivity.

Heat sterilization is the treatment of choice. Instruments should be thoroughly cleansed in order to remove adherent material before heat treatment. Hepatitis B virus has been shown to be inactivated by heat under the following circumstances: (1) boiling water (100°C) for ten minutes, (2) steam under pressure (autoclaving) at 121°C and 15 pounds per square inch pressure for 15 minutes or (3) dry heat (160°C) for two hours.

Other forms of sterilization may be presumed to be effective, although precise information regarding inactivation is lacking. These include chemical disinfectants, such as (1) solutions of sodium hypochlorite, 2.5 percent for 30 minutes, (2) 40 percent aqueous formalin (16 percent aqueous formaldehyde) for 12 hours: formalin, 20 percent in 70 percent alcohol, 18 hours, (3) two percent aqueous alkalinized glutaraldehyde for 10 hours and (4) gas sterilization with ethylene oxide (refer to manufacturer's recommendations).

Prophylaxis: Gamma Globulin

Immune serum globulin has been found to be effective prophylaxis following exposure to hepatitis A. It is, of course, important to establish that close contact with the infected person has occurred (including food sharing, kissing, sexual intercourse or contamination with blood, urine or stool) before administering gamma globulin.

A hyperimmune globulin containing high levels of antibody to hepatitis B surface antigen has recently been developed and has undergone controlled prospective experimental trials. These studies have shown the efficacy of this product for at least six months after exposure. The material is now commercially available as a licensed product for hepatitis B exposure after needle stick inoculation.

Household Contacts

Spouses and other intimate contacts of patients with hepatitis are at greater risk for hepatitis transmission than are more distant contacts. It is important that those exposed persons realize the possibility of hepatitis transmission by blood and other bodily fluids. Good personal hygiene, especially hand washing, should be practiced, and materials contaminated with blood, urine, stool or saliva should be disposed of or disinfected. Razors, toothbrushes, eating utensils, towels and washcloths should not be shared.

Hospital Contacts

Within the hospital setting, patients with hepatitis should be cared for in an area in which blood and other body fluids can be handled with care. When handling blood or blood contaminated materials from HB_sAg positive patients or patients with suspected infectious liver disease, staff members are advised to wear gloves and gowns. During procedures in which blood or other body fluids might splash or splatter, a mask is appropriate. Disposable syringes and needles should be used and blood specimens should be labeled "hepatitis."

Laboratories

Hepatitis transmission is especially likely to occur wherever blood specimens are to be found. Consequently, clinical laboratories, hematology and serology laboratories, hepatitis research laboratories and autopsy laboratories are at special risk. Accidental needle pricks or ingestion of serum specimens at the time of mouth pipetting may result in the transmission of infective material. Contamination can also occur during vigorous shaking of specimens, aerosolization, homogenizing, or opening screw cap bottles. Blowing out the final drops of serum from a pipette or pouring fluids vigorously or centrifuging tubes that are not carefully closed creates additional hazards. Mouth pipetting, eating and smoking in the laboratory should be prohibited. Use of protective clothing, including gloves, gowns or similar garments, is sound laboratory practice. If there is danger of splashing or aerosolization, a mask should be worn. However, masks, gowns or robes should not be considered a substitute for careful technique. Laboratories should insist that specimens coming from hepatitis patients be labeled "hepatitis." Materials collected for inactivation and disposal should be labeled "biohazard."

Hemodialysis Units

It is recommended that patients and staff be continually screened for hepatitis B virus (HBV) infection. Monthly determinations of HB_sAg and anti-HB_s, as well as serum glutamic pyruvic transaminase (SGPT), are appropriate for a modern hemodialysis unit, especially when HBV spread has been documented within the unit. "Clean units," free of HBV, may only require screening at two-to-four month intervals. New hemodialysis patients and staff should be routinely screened for HB_sAg and anti-HB_s before admission to the unit.

Within hemodialysis units gowns should be worn and changed regularly. These gowns should not be worn outside the unit. Gloves should be worn during procedures when there is contact with blood or when a dialysis machine is being cleaned or dismantled. A fresh pair of gloves should be used with each patient. (When splattering of blood or aerosolization is likely to occur, a mask is appropriate.) Cuts and abrasions should be bandaged to protect from contact with infected material.

HB_sAg positive patients should be separated from other patients who lack HB_sAg. If possible, and practical, staff should be separately assigned to HB_sAg positive and HB_sAg negative patients. Staff with anti-HB_s preferentially should be assigned to HB_sAg positive patients. Those who lack anti-HB_s should be assigned to those patients who are HB_sAg negative. If the antigen-antibody status of a patient is not yet known, the patient should be managed in separate areas from other patients within the unit. Equipment that cannot be heated or gas sterilized should be decontaminated in a liquid bath, if possible, or thoroughly washed to remove adherent material and to dilute out any viral particles.

Mental Institutions

Endemic and epidemic viral hepatitis frequently occurs in institutions for the mentally retarded. In these institutions both patients and staff are at risk. Practical recommendations include the following:

- In institutions where hepatitis B infection has been shown to be endemic, periodic screening of residents and staff is appropriate.
- Staff members responsible for the care of

the mentally retarded should be trained and warned to use good hygienic practices.

- Open wounds likely to have contact with blood or contaminated materials should be covered.
- Personal toiletry articles, such as razors or toothbrushes, should not be shared.
- Medical and paramedical personnel, including physicians, dentists and laboratory workers who will be involved with the care or evaluation of HB_sAg positive patients, should be advised of the antigen status of the patients so that appropriate precautions can be taken in patient care and specimen handling.

Nursing Homes

Since patients from mental institutions, or other closed populations, are more likely to harbor HB_sAg, it is important to determine the patient's antigen status before admission to the chronic care facility. Information on antigen status can then be used by personnel at the second institution to enforce appropriate precautions in specimen handling and patient care. Naturally, the HB_sAg status of a patient should not prevent giving appropriate care to the patient.

Management of HBsAg Positive Health Care Workers

It is officially recommended that "the presence of HB_sAg is sufficient reason for personal precautions but not necessarily evidence of a substantial hepatitis risk for contacts or associates" and "health personnel observed to be HB_sAg positive should not be restricted from patient contact solely on the basis of this serologic finding."[47] It is therefore of utmost importance that efforts be made to prevent unreasonable management or misunderstandings of the risks associated with health care workers found to be HB_sAg positive. Since minor hand injuries are thought to be the source of infected blood which may be introduced by oral or percutaneous routes, scrupulous aseptic technique and the use of gloves in minor surgical procedures, dental procedures and wound dressing are recommended. Some persons who have persistent HB_sAg findings may become negative for HB_sAg after six or more months of positivity. Therefore, each person with positive findings should be tested periodically at six-month intervals to determine whether or not the antigen continues to persist. SGOT and SGPT should also be tested to rule out underlying acute or chronic liver disease. If the SGOT and SGPT values are normal, repeat tests are justified in subsequent months.

Persons working in oncology units and hemodialysis units may be at risk for the development of the HB_sAg carrier state, and it is appropriate to routinely test such people for HB_sAg.

Food Handlers

Transmission of hepatitis B by food, although possible, has not been definitively documented. It is, however, wise to prevent food handlers with acute hepatitis B from working while active liver disease is present. Chronic HB_sAg carriers should be educated about transmission and the need for good personal hygiene and avoidance of hand injuries.

Pregnancy

Some women with acute hepatitis B during pregnancy may transmit infection to their infants. This occurs especially when hepatitis develops in the third trimester. The baby may become HB_sAg positive four to eight weeks after birth and then persistent HBSAg may develop, eventually leading to low grade chronic liver disease. Some initial studies suggest that hyperimmune gamma globulin may be efficacious in preventing the antigen carrier state in newborn infants. It is appropriate that pregnant women be screened for anti-HB_s and, if they lack antibody, should avoid working in high risk environments or should be transferred to work areas where the risk of hepatitis transmission is lower.

Pathology

The gross and histologic appearances of hepatitis A, B and non-A non-B hepatitis in man are similar. The disease is diffuse throughout the liver and characterized by liver cell necrosis associated with an active inflammatory infiltration of leukocytes and histiocytes. Necrosis is more pronounced in the central portions of the lobules and the inflammatory infiltrate is more prominent in the regions surrounding the portal tracts. Fatty change is not a characteristic of this illness. Acidophilic bodies—that is, liver cells showing eosinophilic change—may be seen in the central zonal areas in association with ballooning of cells. Multinucleated giant cells may also be present. A cholestatic component may be found in the central portions of the lobules and may be seen in up to 20 percent of patients. The architecture of the

liver is generally well preserved. Severe disease may be characterized by submassive necrosis showing bridging areas of necrosis linking portal tracts to central veins or portal tracts to portal tracts. This bridging necrosis carries with it a guarded prognosis and may be associated with a poor prognosis in 50 percent of the patients who will either die or in whom chronic liver disease will develop. In this situation, the recticulum may collapse and the liver lobule may lose its supporting structure. Eventually, fibrosis may develop in those patients who survive. Special stains such as the orcein stain may show ground glass cells containing HB_sAg.

Treatment

Traditionally treatment for these illnesses is nonspecific. The basis of treatment is rest with bathroom privileges. Until the course of the illness has declared itself it is often wise to recommend strict adherence to rest because it is unclear in which patients fulminant failure may develop. As improvement occurs, increased activity can sometimes be tolerated during the convalescent period, but not until the patient is symptom free and the liver has lost its tenderness. Biochemical criteria for liberalization of the patient's management generally should include a bilirubin value below 2 mg per 100 ml and alanine amino transferase (serum glutamic pyruvic transaminase) levels less than four times the upper limit of normal. A low fat diet high in protein is generally more palatable for patients who are symptomatic and is less likely to produce nausea. There is no real benefit or harm from a regular diet and often it is wise to allow the patient to eat in accordance with the degree of anorexia or nausea. Corticosteroids are not helpful in the treatment of acute hepatitis or in the treatment of severe acute hepatitis such as that associated with bridging necrosis. Hypotheses suggesting that steroids may be helpful in the management of viral hepatitis have been refuted. During the acute phase of illness it is often wise to see the patient at least once a week until it is clear that the patient is improving. After that time, the patient may be seen at less frequent intervals. If jaundice or symptoms recur or the liver enlarges, the patient should be reevaluated to determine if chronic liver disease is developing. Most patients can be managed at home but occasional patients may require hospital treatment. This should be reserved for those patients at greatest risk for the development of fulminant failure. Accordingly, all patients with early signs of encephalopathy would merit admission to hospital. Similarly, patients with falling prothrombin concentrations or patients with high bilirubin levels in excess of seven times normal in association with normal or small liver spans would benefit from hospital admission since these criteria connote a guarded prognosis. Once a trend towards biochemical and clinical improvement clearly has been shown in patients with severe illness, convalescence at home may be begun.

The Past and the Future

A decade has passed since a geneticist published his evaluation of protein alterations among multiply transfused patients. In these studies Baruch Blumberg described the discovery of a precipitating antibody in the serum of a patient with hemophilia. The antibody was directed against an antigen first found in the serum of an Australian aborigine. Within the next four years it became apparent that this antigen/antibody system, which initially had been found in the sera of patients with malignant lesions and subsequently with Down syndrome, indeed had its closest association with hepatitis. Various names have been used for the antigen on the surface of the virus particle, including Australia antigen, hepatitis associated antigen and, most recently, hepatitis B surface antigen.

This decade has seen the first description of the morphology of hepatitis B virus. The DNA core of the virus was found and its antigenic properties assessed. Recently another surface antigen, the "e" antigen, has been described. Three antigens, therefore, have been associated with the hepatitis B virus particle or Dane particle. On the virus surface is the Australia or hepatitis B surface antigen. The core antigen consists of viral DNA. The persistence of "e" antigen suggests the development of chronic disease and the presence of "e" antigen suggests a high degree of infectivity.

The ability to detect the presence of the virus allowed scientists to investigate the pathogenesis of associated syndromes such as periarteritis and glomerulonephritis as well as the hepatic sequelae of hepatitis such as chronic persistent hepatitis, chronic active hepatitis, postnecrotic cirrhosis and hepatocellular carcinoma. An experimental hepatitis B vaccine has recently been developed and the efficacy of hyperimmune gamma globulin prophylaxis has been tested. The past decade has

fostered rapid advances in hepatitis research but also has opened many new challenges. A multitude of unanswered questions await the efforts of physicians and other scientists of the future.

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Specialty Conference

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Refer to: Kirkpatrick SE, Corrin A, Higgins C, et al: Differential diagnosis of congenital heart disease in the newborn—University of California, San Diego, School of Medicine, and University Hospital, San Diego (Specialty Conference). West J Med 128:127-132, Feb 1978

Differential Diagnosis of Congenital Heart Disease in the Newborn

STANLEY KIRKPATRICK, MD:* *In the newborn nursery it is frequently a problem to determine the presence or absence of congenital heart disease. We have endeavored to develop a simplified approach to alert nursery physicians or nurses to the possibility of underlying congenital heart disease and its differentiation from other causes of cyanosis, including pulmonary parenchymal disease. This problem will be illustrated by the case presentation.*

ADALINE CORRIN, MD.† The infant was a boy born to a 24-year-old gravida 2, para 1, aborta 1 mother. The pregnancy was complicated by a positive Venereal Disease Research Laboratories test (VDRL) in the first month of pregnancy; treatment was carried out with penicillin. The baby had Apgar scores of 7 and 8 at one and five minutes. He was meconium stained at birth. The weight was 5 pounds 3 oz and the baby was judged to have been born at approximately 35 weeks gestation. Immediately after birth the baby was noted to be tachypneic. Initial heelstick blood gas values were: pH 7.36, carbon dioxide pressure (Pco_2) 46 and oxygen pressure (Po_2), 37 mm of mercury. He was treated with 40 percent oxygen by hood and repeat gas values were pH 7.36, Pco_2 40 and Po_2 64 mm of mercury. The findings on the initial roentgenogram of the chest were not clearcut. They were interpreted as being consistent with either increased pulmonary venous markings or meconium aspiration. At four days of age he began to have more retractions and grunting, and his color was more dusky. He was transferred to University Hospital, San Diego.

On arrival the baby was in moderate respiratory distress. The respiratory rate was 80 to 100. There were nasal flaring, grunting and intercostal retractions. Rales were heard over both lung fields. The heart rate was 140 to 150 beats per minute. The second sound was closely split and the intensity of the pulmonic second sound (P_2) was accentuated. There was a continuous murmur best heard in the second and third left intercostal spaces and in the infraclavicular area on the left. Pulses were normal. The blood pressure was 61 mm of mercury in the left arm, 72 left leg and 65 right leg. The liver was palpated 2 to 3 cm below the costal margin.

The leukocyte count was 7,100 per cu mm and the hematocrit 44 percent. Cultures for bacteria were negative. The IgM was 15. Titer for cytomegalovirus (CVM) was 1:64, varicella, less than 1:8 and herpes simplex 1:32. The VDRL was nonreactive. X-ray studies of the chest were confusing and will be discussed by Doctor Higgins. An electrocardiogram showed a right axis deviation and peaked P waves, consistent with cor pulmonale. Treatment was continued with penicillin and gentamicin. Tachypnea and intermittent retractions, flaring and grunting continued. A cardiac catheterization showed pulmonary venous desaturation. Right ventricular and main pulmonary artery pressures were elevated to systemic levels. There was a small patent ductus arteriosus and a patent foramen ovale. Following catherization, the murmur decreased to a pronounced degree, and on an x-ray film of the chest more infiltrate was seen on the right than on the left. The infant

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TABLE 1.—*The Five Cardinal Findings in Infants With Congenital Heart Disease*

- Heart murmur
- Congestive heart failure
- Cyanosis
- Abnormal heart rate
- Tachypnea

did well in room air, and gas values were Po_2 42 and Pco_2 46 mm of mercury.

WILLIAM NYHAN, MD, PH D:* *Thank you, Dr. Corrin. You indicated that the x-ray studies of the chest were somewhat confusing. Let us turn now to Doctor Higgins for a discussion of these roentgenograms.*

CHARLES HIGGINS, MD:† The initial x-ray films of the chest showed a large increase in the interstitial markings in the right lung. All of the vessels were indistinct, particularly on the right side, indicating a substantial interstitial and alveolar filling process. There was more infiltrate in the right lung than in the left, a fact that is somewhat atypical for congestive heart failure, but certainly not something that is never seen. There was a large heart. The cardiothoracic ratio was over 60 percent. There was also a small right pleural effusion. The pulmonary findings suggested a diagnosis of aspiration pneumonia, but an enlarged heart is usually not seen in aspiration pneumonia, even in severe instances. In a large series of patients with meconium aspirations the cardiothoracic ratio was below 60 percent in almost all patients.

A radiograph obtained two days later showed persistent infiltrate in the right lung, but almost complete clearing on the left side. The heart size was still somewhat enlarged. Of course, clearing of infiltrate on the left side, along with persistent infiltrate on the right side was more in keeping with an aspiration pneumonia. Most cases of aspiration pneumonia clear within three days. Many are clear within 24 hours on x-ray studies. A film obtained one day later showed the left lung almost normal and the right lung with some persistent infiltrate. The heart size had decreased slightly. The most recent film obtained showed some persistent infiltrate in the right lung, a normal-sized heart and a normal pulmonary parenchymal pattern on the left.

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DR. NYHAN: *Thank you, Dr. Higgins. Let us now turn to Dr. Kirkpatrick for a discussion of this problem.*

DR. KIRKPATRICK: The identification of those infants who are at increased risk for congenital heart disease is important so that they may be selected for a more careful cardiovascular examination.[1] In the general population the incidence of congenital heart disease is approximately eight per 1,000 live births and does not vary with race. Infants born to diabetic mothers have an increased risk of congenital heart disease.[2] Also at increased risk are twin infants, children with chromosomal abnormalities and babies born to mothers who have congenital heart disease. In these specific instances an infant requires special attention to the possibility of congenital heart disease.

There are five cardinal findings (Table 1) that suggest the presence of significant heart defects: (1) heart murmur, (2) congestive heart failure, (3) cyanosis, (4) abnormal heart rates and (5) tachypnea.

Heart Murmur

Heart murmurs (Table 2) are not easily heard in the noisy nursery, particularly when the infant is being monitored with an auditory signal and receiving assisted ventilation. Quiet surroundings are needed in order to auscultate adequately. If the child cannot be taken to a quiet place, then it is important to make the surrounding area as noise-free as possible. A murmur, heard at the newborn examination shortly after birth, when pulmonary vascular resistance is still high and pulmonary pressure is essentially equal to systemic, indicates that the underlying lesion is most likely obstructive or an insufficient valve. The diagnoses to be considered are aortic stenosis,

TABLE 2.—*Relationship of the Type of Cardiac Defects and the Age at Which the Murmur Is First Noted*

Age	*Defect*
Birth	Obstructive lesions with pressure gradient: aortic stenosis, pulmonary stenosis, coarctation, regurgitant A-V or semilunar valves MI, TI, AI, PI.
Discharge from nursery	All of the previous lesions. Left to right shunts as pulmonary vascular resistance drops: ventricular septal defect, patent ductus arteriosus.
Routine 6-week visit	Left to right shunts more pronounced with further drop in pulmonary vascular resistance.
4 to 6 years	Atrial septal defect.

pulmonic stenosis, and mitral or tricuspid regurgitation. Coarctation of the aorta is more likely to be found a little later when the patent ductus arteriosus is fully closed. Murmurs in the immediate newborn period rarely indicate the presence of a left to right shunt since the pressures and resistances are very nearly equal in the right and left heart chambers.

As the pulmonary vascular resistance and pressure begin to fall, murmurs resulting from left to right shunts appear. Therefore, if no murmur was noted at the initial newborn examination but one is found at 3 days of age, the possibility of a ventricular septal defect or a pathologic patent ductus arteriosus should be considered. It is possible to hear a nonpathologic continuous murmur in infants during the first 24 hours which then disappears on the following day as the ductus closes physiologically.

At the six week evaluation, the pulmonary vascular resistance has dropped sufficiently so that a left to right shunt through a ventricular septal defect will be apparent. In contrast, the murmur of an atrial septal defect is usually first noted at 4 to 6 years of age. It is more common in these children for there to be a gradual increase in their left to right shunt over a period of years because of the minimal gradient across the atrial septum and the compliance characteristics of the two ventricles.

Congestive Heart Failure

The signs and symptoms of congestive heart failure in the newborn period are distinctly different from those seen in adults.[3] Peripheral edema, a very common finding in adults with congestive heart failure, is a late sign in infants. The initial signs of failure in infants are usually respiratory distress, tachycardia, inappropriate weight gain and an enlarged liver. The nurses will frequently indicate that the infant is a poor feeder with an above average respiratory and heart rate. The color may be poor and the urinary output decreased. Any such infant should be examined carefully for the possibility of congenital heart disease. Infants with congestive heart failure commonly have a very consistent heart rate of 160 to 180 because of a predominant sympathetic discharge which also helps to explain the diaphoresis often seen in these children.

The liver in the newborn infant is virtually always palpable and may be as much as 3 cm below the right costal margin normally. It is important to distinguish between a liver that is displaced inferiorly and a liver that is truly enlarged because of congestion from heart failure. In the latter instance, the liver may be boggy or firm and have a blunted edge which is frequently directed posteriorly. Children with respiratory distress may have flattened diaphragms and livers which are displaced inferiorly but their consistencies and edges are entirely within normal limits.

Gallop sounds are often heard in small infants who have congestive failure if the examiner is patient and listens in a quiet atmosphere. Rales in the lung fields are often present, and they appear in both right-sided and left-sided heart failure. Pulmonary edema as a sign of primary left heart failure and liver engorgement as a sign of primary right heart failure are less reliable in infants than in adults. It is most common for there to be concomitant evidence of both right and left heart failure in infants.

Since the newborn myocardium is functioning at the peak of its ventricular function curve, it does not tolerate volume overload well. Consequently, common causes of congestive heart failure in the newborn include diagnoses such as arterial venous fistulae, maternal-fetal or twin-twin transfusions, and rapid volume expansion from an indwelling catheter, all of which represent volume overload. Various forms of congenital heart disease do not usually cause failure at or shortly after birth but there are a few exceptions, such as tricuspid regurgitation, absent pulmonary valve, supraventricular tachycardia and hypoplastic left heart syndrome with early closure of the ductus arteriosus.

Neonatal asphyxia with resultant acidemia, hypoglycemia and hypocalcemia can precipitate myocardial failure. An uncommon cause of failure is embolization of the coronary artery which results in myocardial infarction during or shortly after delivery.[4] Myocardial infarctions in infants present with an electrocardiographic pattern which is quite diagnostic. Anomalous left coronary artery may also cause infarction in infants; however, symptomatology usually occurs after a week of life when pulmonary arterial pressure and resistance have dropped to levels which provide inadequate coronary profusion.

Cyanosis

The third major finding in infants with congenital heart disease is cyanosis (Figure 1). There are three types of cyanosis: central, peripheral

and differential. Central cyanosis is characterized by arterial desaturation within the aorta. Peripheral cyanosis, on the other hand, simply indicates stasis of blood flow in the periphery with greater than 3 grams per 100 ml of desaturated hemoglobin. It does not mean that there is desaturation within the central aorta. Most of these patients are cool peripherally, and warming usually restores normal color.[5] Differential cyanosis virtually always indicates congenital heart disease. Coarctation is usually part of the complex. If the upper part of the body is pink and the lower body blue, this indicates a coarctation of the aorta with oxygenated blood supplying the upper body and desaturated blood supplying the lower body via retrograde flow through the ductus. A patient with transposition, coarctation and retrograde flow through a patent ductus arteriosus shows the reverse situation with the lower portion of the body pink and the upper portion blue. Simultaneous determinations of oxygen saturation in the right brachial artery and the femoral artery are helpful in confirming the presence of differential cyanosis.

Central cyanosis results from either an abnormal hemoglobin (methemoglobinemia) or from a failure of hemoglobin to come in contact with oxygen. The diagnosis of methemoglobinemia as a cause of central cyanosis is usually easily made, providing one thinks of the possibility. Normally, when heparinized venous blood is exposed to room air it becomes pink. In persons who have methemoglobinemia, the blood remains dark. A suspicion of methemoglobinemia is confirmed by obtaining a saturation and a Po_2 in the blood gas laboratory. This analysis will show a normal partial pressure of oxygen and a low oxygen saturation. The definitive diagnosis can be made by electrophoresis.

For the purposes of discussion, let us assume that the above mentioned forms of cyanosis have been ruled out, and we are left with a patient who has a low oxygen saturation in both the upper and lower extremities while breathing room air. The next step is to carry out ventilation in the child using 100 percent oxygen and obtain arterial blood gas values again. I prefer that ventilation in the neonate be done by mechanical means, either via endotracheal tube or mask, so that the possibility of inadequate ventilatory effort is excluded. After equilibration, repeat blood gas determinations are obtained. If the Po_2 and oxygen saturation are essentially unchanged, this indicates the presence of blood bypassing the lungs, as occurs in infants with congenital heart disease and a right to left shunt. If, on the other hand,

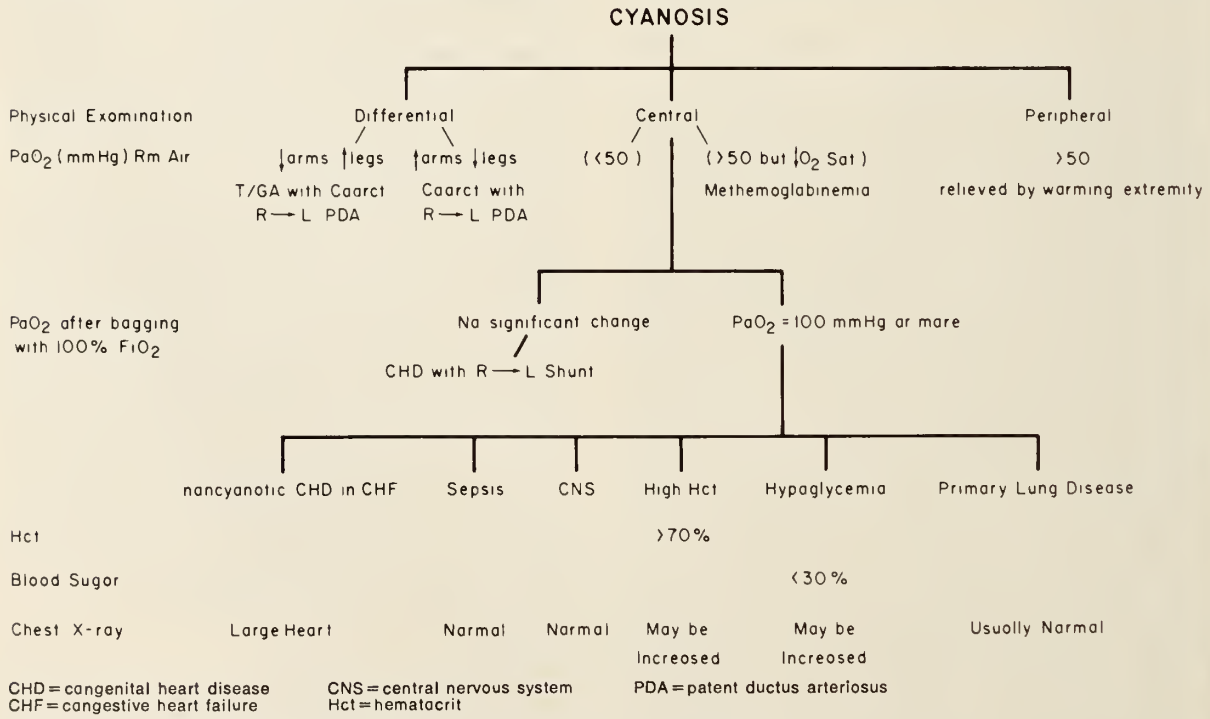
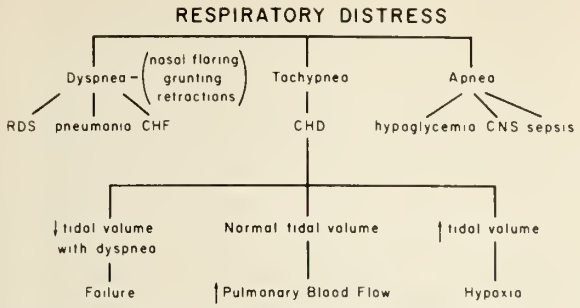


Figure 1.—Flow chart for the evaluation of cyanotic patients. Tests to be done are listed at the left. A patient's response to each of these tests leads along the line to the proper diagnosis.



CHD = congenital heart disease CNS = central nervous system
CHF = congestive heart failure RDS = respiratory distress syndrome

Figure 2.—Differential diagnosis of respiratory disease. Analysis of aspects of respiratory distress which are useful in the diagnosis of specific disease entities.

a significant rise in oxygen saturation is seen such that the Po_2 reaches 100 mm of mercury or greater, the infant most likely has primary pulmonary disease. However, some infants who have acyanotic congenital heart disease with congestive heart failure may show significant improvement with assisted ventilation. These infants can usually be differentiated from those with pulmonary disease by the presence of cardiomegaly in roentgenograms.

Heart Rate

The fourth cardinal finding that heralds the presence of congenital heart disease is an abnormal heart rate which may either be excessively fast or unusually slow. When the heart rate is 240 to 300 (paroxysmal supraventricular tachycardia), congestive heart failure will develop because of inadequate time for diastolic filling. If the heart rate is 50 or below the infant will have congestive heart failure because of inadequate cardiac output. Although stroke volume increases remarkably, cardiac output is still insufficient to meet the child's demands because the heart rate is so slow. Our current mode of therapy for paroxysmal atrial tachycardia is electroconversion using 1 to 2 watt seconds per kg of body weight.

Following conversion, digitalis is given and administration of the usual dose of digoxin (Lanoxin®), 12 to 15 μg per kg of body weight in divided doses every 12 hours, is maintained. Treatment for the infant with complete congenital heart block and a heart rate of 50 or less is permanent pacing. If, on the other hand, the heart rate is 60 or greater, it is likely that stroke volume will increase sufficiently to meet demands for growth. The prognosis for patients with paroxysmal atrial tachycardia or complete heart block is much better if there is no associated congenital heart disease.

TABLE 3.—*Diagnostic Aids in Differential Diagnosis of Congenital Heart Disease*

History and physical examination
Hematocrit, electrolytes, calcium, glucose studies
Blood gas determinations on room air and bagging with 100 percent forced inspiratory oxygen
X-ray film of the chest
Electrocardiogram
Echocardiogram
Cardiac catheterization

Tachypnea

The fifth finding that alerts to the possibility of congenital heart disease is an abnormal respiratory rate (Figure 2).[6] Isolated tachypnea is the most common pattern. If the child is in congestive heart failure, dyspnea will be among the clinical features. On the other hand, if dyspnea is the primary finding with flaring of the alae nasi, retractions and grunting, primary pulmonary disease is the more likely cause.

Once one of the five cardinal findings of congenital heart disease has been recognized, our workup consists primarily of the studies listed in Table 3. Careful assessment of the peripheral pulses is a simple procedure worth emphasis. It must be a part of all cardiac evaluations. The diagnosis of coarctation of the aorta is made if femoral pulses are absent. If the pulses are bounding in a premature infant a diagnosis of patent ductus arteriosus may be strongly suspected. The second physical finding that should be emphasized is the position of the liver. A horizontal liver or a liver on the same side as the cardiac apex should raise the question of visceral heterotaxy and the associated asplenia-polysplenia syndrome.

Helpful Radiographic Findings

There are five aspects of roentgenograms that have been significantly helpful in the diagnosis of congenital heart disease. The first is the presence of a right-sided aortic arch. This finding, in association with decreased pulmonary blood flow, is indicative of tetralogy of Fallot. A right aortic arch in the presence of increased pulmonary blood flow suggests a truncus arteriosus or transposition of the great arteries. Differential pulmonary blood flow, the second sign, can be seen in persons with tetralogy of Fallot, hemitruncus and absence of

one of the pulmonary arteries. The third sign is a characteristic shape of the heart, which is often helpful when present. The egg-on-egg appearance with a narrow base is typical of transposition of the great arteries, and a boot-shaped heart with concavity of the pulmonary outflow is consistent with tetralogy of Fallot. An abnormal position of the cardiac apex, the fourth sign, is seen in the scimitar syndrome[7] or the asplenia-polysplenia syndrome. Last, pulmonary vascular markings indicate the amount of pulmonary blood flow. In a patient with a large main pulmonary artery, increased pulmonary arterial markings would indicate an atrial septal defect, while normal pulmonary arterial markings are consistent with pulmonary valvular stenosis.

Helpful Findings on Electrocardiograms

Newborn infants normally have a right ventricular pattern reflecting intrauterine hemodynamics in which the right and left ventricular pressures are the same. At birth, an electrocardiogram in an infant usually shows balanced right and left precordial forces and apparent right ventricular hypertrophy, compared with the adult pattern. Abnormal right ventricular hypertrophy is usually seen in forms of congenital heart disease, such as transposition of the great arteries, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, pulmonary stenosis, double outlet right ventricle, arteriovenous fistula and total anomalous pulmonary venous return. If one sees, on the other hand, a left ventricular predominance, a diagnosis of tricuspid atresia should be suspected. Patients who have a counterclockwise superiorly oriented frontal plane loop often have an endocardial cushion defect. An infarction pattern in the newborn is not common; it is diagnostic of coronary embolism.[4] An anomalous left coronary artery arising from the pulmonary artery does not cause an infarct pattern until several days of life when pulmonary pressure and resistance have dropped sufficiently to provide inadequate coronary perfusion.

Echocardiography is a relatively new modality which has become invaluable in cardiac evaluation. Catheterization and angiography continue to be the most reliable tools in the diagnosis of congenital heart disease, and definition of intracardiac anatomy.

In summary, there are five major findings in the newborn period that should alert a nurse or physician to the possibility of congenital heart disease. These are heart murmur, congestive heart failure, cyanosis, abnormal heart rate and tachypnea. It is important to obtain simultaneous upper and lower compartment blood gas determinations while the patient is breathing room air and 100 percent oxygen. If there is a significant increase in the Po_2 while the patient is breathing 100 percent oxygen, the infant most likely has primary pulmonary disease. On the other hand, if there is little or no increase in oxygen saturation while the patient is breathing 100 percent oxygen, the presence of congenital heart disease must be ruled out.

DR. NYHAN: *In the case presented did you feel that the baby had congenital heart disease?*

DR. KIRKPATRICK: I did not feel that there was underlying congenital heart disease in this baby. The x-ray chest film showed evidence of increased markings, more on the left. On physical examination there was a soft ejection murmur with normal splitting of the second heart sound and no flow murmur. I believe the findings represented an increase in arterial blood flow to the left lung because it was the least involved with primary pulmonary disease.

Clinically our major concern was to rule out the presence of pulmonary venous obstruction. With the normal chamber sizes noted on echocardiograms, we felt we had ruled out a significant left to right shunt. During the catheterization I placed the catheter into the pulmonary veins without difficulty and found pulmonary venous pressure to be normal. The major decrease in pulmonary venous saturation was noted in the area of the lung which had the most evidence for parenchymal involvement. We felt certain that the patient did not have congenital heart disease and that the desaturation was on the basis of primary parenchymal disease.

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Refer to: Hemochromatosis—Medical Staff Conference, University of California, San Francisco. West J Med 128:133-141, Feb 1978

Hemochromatosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The topic for discussion at Medical Grand Rounds today will be that of hemochromatosis. The case summary will be given by Dr. Guy Weinberg.*

DR. WEINBERG:† The patient is a 43-year-old white man who presented in the fall of last year to the Metabolic Clinic with the chief complaint of impotence. Five years ago the patient noted the onset of difficulty of achieving and maintaining an erection, as well as a reduced sex drive. Two years ago his symptoms had continued and his private physician prescribed hormone pills which increased the sex drive, but caused no change in the performance. A year ago the patient noted the onset of pain and stiffness with slight enlargement in all of his proximal interphalangeal joints, as well as the second and third metacarpophalangeal (MCP) joints. There was no heat or redness. The patient was treated at that time with prednisone, the presumptive diagnosis being rheumatoid arthritis.

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†Guy Weinberg, MD, Medical Resident.

At the time of presentation the patient was completely impotent and had no libido. The rest of the history was noncontributory. Family history indicated that one brother and two sisters had arthritis. On physical examination a II/VI systolic ejection murmur was heard. The patient's testicles were soft and small and there was a female escutcheon and reduced axillary hair. His second and third metacarpophalangeal joints were enlarged but not tender. The initial laboratory studies gave normal findings except for a slightly elevated level of serum glutamic oxaloacetic transaminase (SGOT), a positive rheumatoid factor of 1:320, a serum testosterone value of 101 ng per dl (normal 300 to 1,200), a low serum luteinizing hormone (LH) level of 3 mIU per ml (normal 5 to 25) and a serum iron value of 233 μg per dl (total iron binding capacity, 240 μg per dl).

The patient was admitted for evaluation to the Metabolic Service. Results of a liver biopsy showed 4+ iron on a touch preparation and pronounced iron deposition in the parenchyma with focal periportal fibrous tissue. Findings on x-ray films of the hands will be described subse-

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CPPD = calcium pyrophosphate dihydrate
FSH = follicle-stimulating hormone
LH = luteinizing hormone
MCP = metacarpophalangeal
SGOT = serum glutamic oxaloacetic transaminase
TSH = thyroid-stimulating hormone

quently. Prolactin, thyroid-stimulating hormone (TSH) and cortisol levels were normal. During insulin induced hypoglycemia there were normal responses of hydrocortisone, growth hormone, adrenocorticotropic hormone (ACTH), but a flat curve for both LH and follicle-stimulating hormone (FSH). The patient has been treated by weekly phlebotomy of 500 ml for the past four months. The hematocrit reading has remained stable, but the iron/total iron-binding capacity saturation is now about 85 percent. The patient receives testosterone once or twice a month and has noted a pronounced increase in sexual interest and performance. We have been able to measure iron/total iron-binding capacity in only one sister. Her saturation of iron-binding capacity was about 65 percent.

DR. SMITH: Thank you, Dr. Weinberg. The diagnosis of hemochromatosis is obvious as presented now; it certainly was not so at the time the patient was first seen. Dr. Guy Weinberg is to be congratulated in making this diagnosis at a comparatively early stage. In summary, this patient had two main symptoms. The first of these, and the most important from his standpoint, was impotence of five years' duration. The second was an ill-defined type of arthritis diagnosed as rheumatoid arthritis. He had noted some slight darkening of the skin, but again this was more evident in retrospect. When the diagnosis was suspected, appropriate studies were carried out which clearly showed iron overload by a number of techniques, both direct and indirect. Further studies showed that the areas of injury due to iron overload were confined largely to the endocrine system with pituitary-gonadal insufficiency and to a lesser degree to certain joints. Notably, there was no "bronze diabetes" and no cirrhosis. Fortunately the diagnosis was considered very early despite the atypical presentation of the disease. Appropriate treatment has been instituted and the outcome should be very favorable.

Most endocrine and metabolic diseases are disorders of "too much" or "too little." Hemochromatosis is a unique genetic disorder, or possibly a group of disorders, marked by an inappropriate avidity for the absorption of iron. In the normal adult there is approximately 3 to 4 grams of iron. In hemochromatosis this may be increased ten times. The absorption of approximately 1 mg of iron per day maintains normal health. The absorption of only 3 mg per day leads to hemochromatosis. The extra ingredient is time, measured not in days, weeks or months, but in years. It is this phenomenon of continued excessive absorption of a metal with which we shall be concerned during this presentation.

There are certain key questions which we would like to be able to answer in a discussion of hemochromatosis: (1) What is the genetic transmission of this disorder, or possibly group of disorders? (2) What is the basic cellular or molecular defect which leads to this continued inappropriate absorption of iron? (3) How does excess iron storage injure tissue? (4) What kinds of disorders result from this tissue injury? (5) When should we suspect the diagnosis and how can it be established? (6) How can this disease be treated and what is the prognosis? Obviously there are many subsidiary questions which flow from those listed, but these are quite sufficient to befuddle us in the time available for discussion today.

To understand the abnormalities in iron metabolism in hemochromatosis, we must know something of its normal metabolism. Approximately two thirds of iron is functional. Most of this is in erythrocyte heme, but it is also a constituent of certain enzymes such as catalase, peroxidase and the cytochromes. Another third of iron is in storage form. The major storage form is ferritin, a specialized spherical protein made up of 24 subunits (Figure 1). The apoprotein of ferritin weighs approximately 460,000 daltons. This protein, which may contain up to 23 percent elemental iron in its ferric form, exists as several isoferritins. Another storage form is hemosiderin which probably represents aggregates of partially degraded ferritin, often in an intralysosomal location which is seen as "stainable iron." Approximately 25 to 30 mg of iron per day must be transported through the plasma for the renewal of blood. Transferrin is a specific beta globulin, synthesized largely in the liver for the transport of iron. It carries two ferric ions per molecule

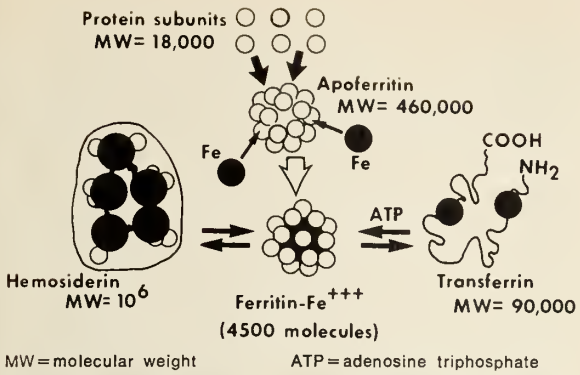


Figure 1.—Iron-binding proteins. Transferrin contains only two molecules of iron, but ferritin may contain up to 4,500 molecules of iron per molecule.

on specific binding sites for use in heme synthesis or deposition into a storage form. The 4 mg of iron that circulates saturates about a third of the binding capacity of transferrin (Figure 2A). Trace amounts of ferritin (mostly apoferritin) also circulate, but are not important in iron metabolism. Although 30 mg of iron passes through plasma daily, only 1 mg need be absorbed from dietary sources to maintain balance.

The total control of iron metabolism lies in its selective absorption.[1] This is obviously very anomalous and precarious. There is no physiological mechanism for the control of excretion, such as exists for calcium, sodium or potassium. Normal iron balance is totally dependent upon the adjustment of absorption from the gut. Approximately 15 mg of iron is ingested daily, and about 1 mg of this is absorbed. This is balanced by the 1 mg net loss in man, primarily through the shedding of epithelial cells in the gut and to a much lesser degree from the skin, and possibly through very minor loss of blood in the normal intestine. In women the average daily loss exceeds 1 mg during the normal reproductive period and may average 1.5 to 2 mg because of menstruation. An additional 0.5 grams of iron is lost during pregnancy. This is balanced by slightly higher gut absorption of iron in women.

There are a number of variables in absorption, only some of which are now understood. Some intraluminal factors are of importance. Iron is absorbed primarily in its ferrous state. Ascorbic acid may serve to reduce ferric to ferrous iron. Hydrochloric acid may increase the solubility of ingested iron. Certain amino acids enhance absorption of iron. Phytates, phosphate and oxalate may reduce iron absorption. The control of iron absorption largely occurs at the levels of the

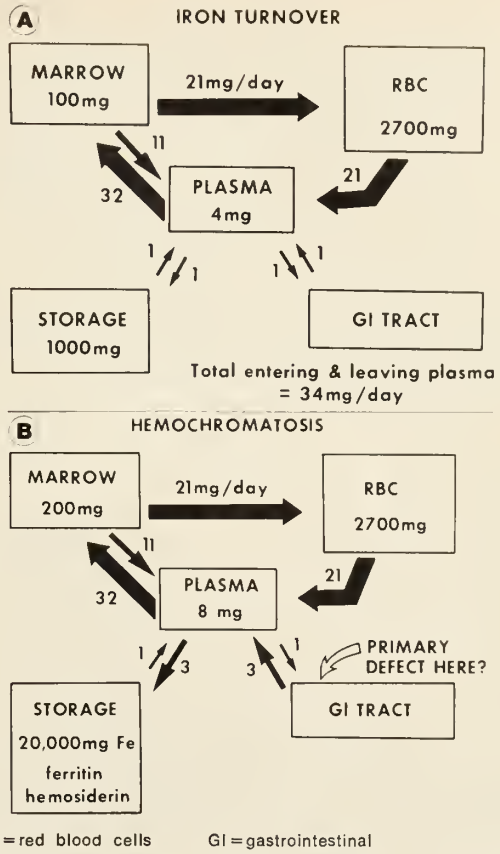
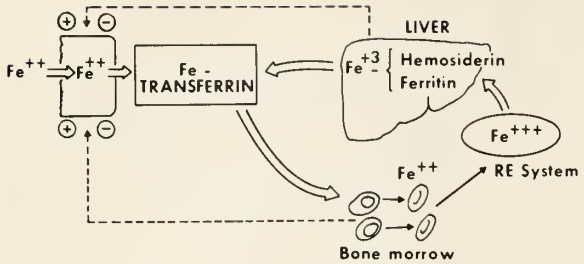


Figure 2.—**A,** Iron pools and turnover in normal man; **B,** Iron pools and turnover in hemochromatosis.

mucosal cell. Dietary iron is absorbed in two forms which have independent absorptive mechanisms. The major form is free iron in its ferrous state, but iron is also absorbed while still complexed in heme. Heme is absorbed intact with its iron later released in the mucosal cell catalyzed by the enzyme heme oxidase. There may be some intracellular carrier protein which mediates rapid transport, but its identity has not been established. Transferrin is not necessary for iron absorption, since excess rather than deficient absorption occurs in the rare patients in whom this transport protein is congenitally absent. Apoferritin has been a major candidate for the presumed intracellular signal which controls the rate of absorption of iron by mucosal cells. When iron is deficient, it is postulated that there is reduced synthesis of apoferritin and enhanced absorption of iron in its ferrous state. When iron is normal or increased there is increased synthesis of apoferritin which traps the iron within the mucosal cell, to be later shed in the normal mucosal cell cycle. Unfortunately cellular levels of ferritin or apoferritin have not always correlated with iron



RE = reticuloendothelial

Figure 3.—Control of iron absorption. Feedback control is exerted from the level of iron stores and from the rate of erythropoiesis.

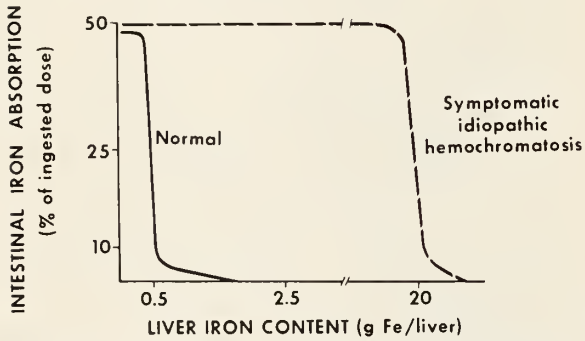


Figure 4.—Regulation of intestinal iron absorption. Regulation occurs in both normal persons and in patients with hemochromatosis, but the latter require much larger iron stores.

absorption. Other carrier proteins for the transport of iron across the mucosal cell have been reported. The chemistry of the transport process is still unclear.

How is iron absorption regulated to insure normal balance (Figure 3)? Two factors at least influence the rate at which the gut absorbs dietary iron: the level of iron stores and the rate of erythropoiesis. These are independent variables. For example, absorption of iron may continue in the face of excess iron stores if there is rapid erythropoiesis. We do not know how these variables create a signal to the mucosal cell to modulate absorption. We do not know whether the primary detection mechanism is in the mucosal cell itself or elsewhere in the body with a secondary signal (chemical ?) transmitted to the gut as the effector organ. Finally, as noted above, we do not know the biochemical response that is elicited in the cell which appropriately regulates the rate of absorption. Since hemochromatosis is probably an inherited disorder of rate control of iron absorption, it seems unlikely that its pathogenesis will be fully elucidated until normal signal-response servomechanisms are better understood.

Hemochromatosis represents continued inappropriate iron absorption, a loss of rate control.[2,3] The rate of absorption may finally return to normal, but only when storage iron has been increased to injurious levels (Figure 4). The site and the mechanism of this breakdown in rate control are not known. Could there be an intrinsic defect in the mucosal cell or a defective signal from an extramucosal receptor? Hemochromatosis has been reported to show different isozyme patterns for ferritin as a possible mechanism for enhanced iron absorption.[4] The significance of these observations is not yet apparent.

As noted, iron absorption may be normal (1 mg per day) in the face of severe hemochromatosis. When iron stores are reduced by repeated phlebotomies, however, iron absorption rises again to pathological levels even though overload still exists. In other words the control mechanisms are still intact, but they are insensitive. Much higher levels of storage iron are required to diminish its dietary absorption. In hemochromatosis, the internal economy of iron—that is, its utilization for red cell production and for the synthesis of heme-containing enzymes—is perfectly normal (Figure 2B). More iron circulates in that transferrin is more nearly saturated. The continued absorption of 3 mg, rather than 1 mg, floods the pool since there is no mechanism for increasing excretion. Storage iron may reach 20 to 40 grams, compared with a normal level of 1 gram. A pathological increase in storage iron is deposited to a disproportionate degree in hemosiderin as compared with ferritin.

Idiopathic hemochromatosis has been considered to be a genetic disease for more than 50 years, although the mechanism of transmission has been debated. Approximately 25 to 50 percent of first degree relatives of patients with hemochromatosis have been found to have some evidence of enhanced iron absorption or of iron overload. Of particular interest is the new information concerning the linkage of hemochromatosis with certain histocompatability loci (HLA).[5] In one study HLA-A3 occurred in 78.4 percent of patients with hemochromatosis (controls, 27.0 percent) and HLA-B14 occurred in 25.5 percent of patients (controls, 3.4 percent). Other studies have confirmed these observations, which tend to confirm the genetic origin of disease and even suggest that the abnormal gene or genes may be

on chromosome 6. New evidence has been obtained that idiopathic hemochromatosis is transmitted as an autosomal dominant disorder, using hepatic stainable iron as the most sensitive marker for the presence of the disease.[6] Since the abnormal gene product is not known, it is necessary to use more remote indices, such as the accumulation of iron, for example. The expression of genetic hemochromatosis is notably influenced by age, since time is required for the accumulation of iron, and by sex because of the physiological phlebotomy of menstruation. Alcohol may also influence the expression of the disease by injury to the iron loaded liver and possibly by further enhancing iron absorption. Finally, we must keep in mind that there may be many different subtypes of hemochromatosis, comparable to abnormal hemoglobins, with heterogeneity in severity and type of phenotypic expression.

Hemochromatosis is a rare disorder, accounting for approximately one of every 7,000 hospital deaths. In its clinical expression it is largely a disease of men (90 percent) because of the normal iron loss in women due to menstruation and pregnancy. In fact, according to current evidence, the genetic defect as opposed to the clinical disorder should be equally as frequent in men and women. Clinical hemochromatosis usually appears late, age 40 to 50, despite the fact that it is a genetic disorder. We assume that the genetic defect itself is not directly injurious. It only alters the ability of the host to cope with dietary iron. Iron overload is a secondary phenomenon which requires many years for its manifestation.

When clinically manifest, hemochromatosis may present with signs or symptoms relating to involvement of the skin, liver, pancreas, heart, endocrine system and joints. Our patient had primarily endocrine and articular symptoms, and we shall begin by discussing these. Increased pigmentation of the skin occurs very frequently in hemochromatosis. This so-called bronzing (actually more slate gray coloring) represents a combination of melanin and iron deposition. Why are the melanocytes stimulated by iron overload? I do not know, and have not seen studies concerning levels of melanocyte stimulating hormone. Diabetes mellitus will be discussed later. Injury to the anterior lobe of the pituitary gland is perhaps the most frequent endocrine abnormality in hemochromatosis,[6] other than its complex relationship with diabetes mellitus. The deposition of hemosiderin in the pituitary results in cell necrosis and fibrosis with no return of function following iron removal. The first clinical manifestation of the pituitary injury is usually of hypogonadism—impotence in the male or menstrual disorders in the female. Laboratory studies show reduced levels of gonadotropins with little or no response to clomiphene or LH releasing factor. The case discussed here illustrates that complication. The secretion of growth hormone may also be reduced. Panhypopituitarism is much rarer. A few cases of hypoparathyroidism and one case of selective hypoaldosteronism have been described and attributed to iron injury.

The arthropathy of hemochromatosis was described comparatively recently (1964)[7,8] despite the fact that it occurs in fully 50 percent of patients with hemochromatosis. It may be the first manifestation of the disease, and as noted it occurred early in the course of our patient. Chondrocalcinosis shown by radiologic studies occurs in approximately 50 percent of cases and hemosiderin is deposited in synovial lining cells and in cartilage. The clinical features are rather nonspecific, which accounts for the usual delay in diagnosis. Pseudogout may occur with calcium pyrophosphate dihydrate crystals associated with chondrocalcinosis. More commonly there is chronic arthritis of the metacarpophalangeal and proximal interphalangeal joints which may superficially resemble rheumatoid arthritis. Some patients have more generalized arthralgias and even polyarthritis. There are interesting and highly suggestive radiographic findings in hemochromatotic arthritis. I have asked Dr. Harry Genant from the Radiology Department, who has been very interested in this topic, to show the x-ray films in this case and to comment at greater length about the radiographic findings in patients with the arthropathy of hemochromatosis.

DR. GENANT:* Arthropathy, as has been indicated, will affect approximately 50 percent of patients with hemochromatosis and will result in an interesting radiographic appearance. In most cases these features are indistinguishable from idiopathic pseudogout or calcium pyrophosphate dihydrate (CPPD) crystal deposition disease. There are, however, some features that occasionally will distinguish the secondary hemochromatotic arthropathy from primary pseudogout.

I shall first discuss the radiographic appearance

*Harry Genant, MD, Radiology Department, University of California, San Francisco.

in the patient presented, and subsequently shall discuss several cases with more advanced disease. The radiographs in this patient are of interest only with respect to the hands. The findings consist of mild periarticular soft tissue swelling involving the proximal interphalangeal and metacarpophalangeal articulations. Mild generalized osteopenia is evidenced by slight thinning of the cortices, particularly in the metacarpals. In addition, a degenerative-like arthropathy with bone proliferation at the metacarpophalangeal and proximal interphalangeal articulations can be seen. These changes are rather subtle and are not those of advanced arthropathy. A close-up view demonstrates slight bone proliferation or overgrowth at several sites and subtle, but definite, cystic changes. This type of involvement of the MCP joints is fairly characteristic of hemochromatosis, although this is early disease. A close-up view of the wrist shows cartilage narrowing associated with the subchondral cyst formation which is fairly characteristic. We do not see the pattern of chondrocalcinosis, or articular calcification, which occurs in about 50 percent of patients with hemochromatosis and arthropathy.

I would like to go on to show more advanced changes in several other cases. In Figure 5 we can see generalized osteopenia that is more severe than in the previous case; the cortices are quite thin. We can see that the metacarpophalangeal articulations are quite abnormal. There is cartilage loss, cyst formation in the metacarpal heads and bone overgrowth. At the wrist we can see articular calcification which represents CPPD crystal deposition in the triangular cartilage which is the usual location. Additionally, we can see mild sclerosis and cartilage loss. A close-up view of

Figure 5.—Roentgenogram of the hand of patient with hemochromatosis. Diffuse osteopenia and calcification of the articular disk of the wrist, associated with arthropathy of the radiocarpal joint.

Figure 6.—Close view of the metacarpophalangeal joints showing joint narrowing, subchondral collapse and striking proliferation of bone, producing a "squared off" appearance.

Figure 7.—Distinct linear and punctate calcification of the fibrocartilage of the lateral meniscus is clearly shown in this magnified view. An associated marginal osteophyte is visible.

the metacarpal heads (Figure 6) shows this fairly characteristic squaring off and teardrop formation. This is probably the most characteristic feature of the hemochromatotic arthropathy. Small cysts can be seen as well.

In idiopathic pseudogout, patients generally present with symptoms in the knees, whereas in hemochromatosis it is more likely that patients will present with symptoms in the hands. In any event, the knees will generally be involved at some point, and what we will see is chondrocalcinosis, fine linear and punctate calcifications, in the fibrocartilage of the meniscus and also in the hyaline cartilage which parallels the articular surfaces (Figure 7). Additionally, we may see arthropathy in the knee—that is, degenerative-like arthropathy consisting of osteophyte formation and subchondral sclerosis (Figure 8). The hips are involved less frequently than the knees and the hands, but may show evidence of articular calcification and also the symphysis may show this dense calcification (Figure 9). Finally, the spine may be involved in hemochromatosis, although it generally does not produce symptoms. We may see fine linear calcifications in the outer fibers of the annulus fibrosis (Figure 10). This again is CPPD crystal deposition, and this appearance simulates syndesmophytosis encountered in ankylosing spondylitis.

In summary, the arthropathy of hemochromatosis is quite similar to that of primary pseudogout, and is characterized by articular degeneration and chondrocalcinosis.

Figure 8.—Anteroposterior roentgenogram of the left knee showing calcification of the medial and lateral menisci, and advanced degenerative changes with marginal osteophytosis, subchondral sclerosis and joint narrowing.

Figure 9.—Striking articular and extra-articular calcification involving the symphysis pubis, hyaline cartilage and labrum of the hip, and the adductor insertions at the ischium.

Figure 10.—Subtle calcification of the annulus fibrosus can be seen in the anteroposterior projection.

Dr. Smith: Thank you, Dr. Genant. Unfortunately, as in the case of endocrine disturbances, the arthritis of hemochromatosis is not improved by removal of iron.

The liver is the major site for iron storage in health. It also receives a disproportionate amount of the iron overload of hemochromatosis.[9] Injury to the liver is frequent and often severe. In the case discussed today this particular complication was not seen. Our discussion of iron metabolism and liver disease will therefore be brief. Characteristically there is slow, chronic progression of liver injury with resulting fibrosis. In comparison with alcoholic cirrhosis, portal hypertension and ascites are less frequent. Hepatoma on the other hand has been reported as occurring in as many as 24 percent of patients with hemochromatosis in whom cirrhosis develops. Liver function may respond to a remarkable degree to iron depletion. Many investigators, particularly in France and in the United States, have noted a strong association between alcohol abuse and the cirrhosis of hemochromatosis. The interplay between alcohol and iron in the genesis of liver disease is still unclear and controversial. There is some evidence that alcohol increases iron absorption and therefore may be additive to the gut defect of hemochromatosis. Possibly iron increases the susceptibility of the liver to injury by alcohol. On the other hand, severe hemochromatotic liver disease has developed in many patients in the absence of any ingestion of alcohol or other known hepatotoxin. One must conclude that iron overload alone is sufficient to produce cirrhosis.

The heart may be involved in hemochromatosis both histologically and clinically.[10] Heart disease has been reported as the cause of death in as many as 30 percent of cases in the older series, but this may no longer be true with more intensive treatment. Deposition of hemosiderin in the heart results in necrosis and fibrosis as in other tissues. There is a greater tendency for ventricular rather than atrial involvement, and for myocardial rather than conducting tissue involvement. The clinical picture may resemble that of a diffuse cardiomyopathy with a large dilated heart. Occasionally there is "restrictive" cardiomyopathy resembling constrictive pericarditis. More rarely tachyarrhythmias and heart block have been described. The iron heart is not a strong heart, but a weak one.

Diabetes mellitus is one of the cardinal manifestations of hemochromatosis. The association is a confusing one, however. Our patient did not have diabetes, so our summary today about this association will be brief and somewhat didactic. Clinical diabetes occurs in the majority of patients with hemochromatosis (65 to 80 percent), but there are some hemochromatotic families without diabetes. Diabetic complications may be frequent with microaneurysms, nephropathy and neuropathy. In studies carried out by Dr. Marvin H. Siperstein, seven of seven patients with hemochromatosis and diabetes had thickening of the capillary basement membrane. An additional patient who did not have diabetes had normal membrane thickness. Some studies have found a high incidence of diabetes mellitus in the relatives of patients who exhibit diabetes in association with their hemochromatosis. As an example, Domack and associates[11] studied the families of patients with hemochromatosis and diabetes and found that 25 percent had diabetes mellitus. In the families of patients with hemochromatosis without diabetes, only 4 percent of the relatives had diabetes. The pathogenesis of carbohydrate intolerance in hemochromatosis is therefore complex.[12] It may represent several things: the carbohydrate intolerance of cirrhosis itself, injury to the pancreatic islets by iron deposition with resultant insulin deficiency, and a genetic cross linkage with diabetes mellitus. Until better markers are found for both diabetes mellitus and for hemochromatosis, their interrelationship will remain obscure.

How can one establish the diagnosis of hemochromatosis? First, the diagnosis should be entertained during the earlier clinical manifestations, as was true in the case discussed today. In addition, family studies should be carried out to detect patients before irreversible injury occurs. All of the laboratory aids for diagnosis are directed toward documenting iron overload. These tests differ in their respective sensitivities. The most sensitive test is directly showing increased hepatic parenchymal iron by liver biopsy, with an increase of stainable iron or an increase on direct chemical analysis.[13] Obviously such a study is rarely done unless one finds other evidence of iron overload, particularly in the serum. In hemochromatosis, serum iron is usually greater than 170 μg per dl and the saturation of transferrin greater than 50 percent. An indirect index of iron overload can be obtained by measuring its urinary excretion after the administration of a standard dose of chelator desferrioxamine

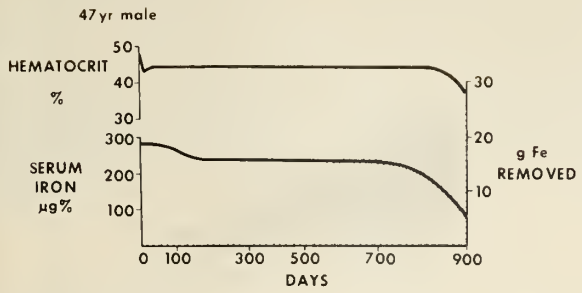


Figure 11.—Response to weekly phlebotomy therapy in hemochromatosis. The shaded area depicts the cumulative iron removed in grams. Note that two years were required to deplete the pathologically elevated iron stores.

(patients with hemochromatosis excrete more than 2.2 mg of iron in the subsequent 24 hours). Serum ferritin may be increased in hemochromatosis, but newer studies show that this does not occur early enough to be a sensitive aid in diagnosis. In summary, increased saturation of plasma transferrin and the direct demonstration of increased hepatic iron by biopsy are the most sensitive indices of the iron overload of hemochromatosis.

How does one treat a patient with hemochromatosis? Fortunately treatment is usually simple and satisfactory. One phlebotomy of 500 ml of blood removes approximately 250 mg of iron. Phlebotomy is repeated once or sometimes even twice a week until the iron stores are depleted, which may require one or two years (Figure 11). Maintenance phlebotomy is then required to balance continued excessive iron absorption. Since this is a genetic disease it is imperative to study patients' relatives in order to find early cases. Iron depletion by phlebotomy clearly prolongs survival.[14] Hemochromatotic liver disease, heart disease and possibly diabetes are improved; endocrine deficiencies and arthritis usually are not. What are the causes of death in those who do die with hemochromatosis? Hepatoma is relatively frequent and unfortunately patients who have hemochromatotic cirrhosis continue to be at risk for hepatoma despite the removal of iron. Recent studies indicate a puzzlingly high association of other neoplasias with hemochromatosis. The reason for this association of iron overload and neoplasia is not clear. Deaths also continue to occur from hepatic failure, variceal bleeding and the vascular complications of diabetes, but such deaths are much fewer in treated as compared with untreated patients.

TABLE 1.—*Unanswered Questions in Hemochromatosis*

- Is the gut mucosal abnormality that enhances Fe absorption primary or secondary to an abnormal signal?
- What is the genetic transmission of the defect or group of defects?
- What is the role of alcohol in the expression of hemochromatosis?
- What is the relationship of the glucose intolerance of hemochromatosis to diabetes mellitus?
- What is the mechanism by which storage iron injures tissue?

In summary, hemochromatosis is a rare genetic disease of the rate control of iron absorption. There are still many unanswered questions concerning it (Table 1). The excessive iron absorption can be suppressed, but only at the cost of a massive overload of iron sufficient to cause tissue injury. Fortunately, if the disease is diagnosed early, as it was in our patient today, it can be adequately treated by phelebotomy and endocrine replacement therapy. A final elucidation of the pathogenesis of hemochromatosis will require new data concerning the mechanisms by which the absorption of iron is normally controlled.

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Important Advances in Clinical Medicine

Epitomes of Progress — Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in anesthesiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the Californa Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Glycopyrrolate: A Challenge to Atropine

ATROPINE, a naturally-occurring belladonna alkaloid, is frequently used during anesthesia as the antimuscarinic drug of choice for premedication, for treatment of bradycardia and, in conjunction with a cholinergic drug, for reversal of the effects of nondepolarizing muscle relaxants. Its popularity persists despite several shortcomings. As premedication its short duration of action (1 to 1½ hours when given intramuscularly) often means that the vagal blocking effects have lapsed before induction of anesthesia; its tertiary ammonium structure allows it to readily cross the blood-brain barrier, resulting in unwanted central effects; and the tachycardia and occasional dysrhythmias following intravenous use may be undesirable and potentially dangerous in some patients.

The search for an antimuscarinic agent without the inherent disadvantages of atropine has led to the synthesis of several quaternary ammonium substitutes. Glycopyrrolate (Robinul®) introduced in 1960, has much to recommend its use over atropine in anesthesia and surgical procedures. Its quaternary ammonium, highly polarized structure does not readily permit passage across the blood-brain barrier, resulting in a greatly reduced incidence of central anticholinergic effects. The longer duration of action (four to six hours when given intramuscularly) favors its use as a premedication to protect against vagal reflexes induced by drugs, intubation or surgical manipulations. A significant reduction in gastric volume and acidity compared with atropine serves to protect against serious sequelae of aspiration.

In the reversal of neuromuscular blocking drugs, glycopyrrolate protects as well as atropine against the muscarinic effects of reversal drugs, with less tachycardia and lower incidence of dysrhythmias. When given intravenously, the duration of antimuscarinic action of glycopyrrolate is three to four hours longer than the duration of cholinergic activity of both neostigmine and pyridostigmine. The incidence of all muscarinic complications is decreased.

Only in the treatment of severe bradycardia, caused by increased vagal tone, may atropine be preferred to glycopyrrolate because of its greater effectiveness in increasing pulse rate. In all other pharmacological actions, glycopyrrolate appears to have decided advantages.

KENNETH S. CHING, MD

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The Pulmonary Artery Catheter for Measurement of Left Ventricular Function

ASSESSMENT of left ventricular performance and reserve is important for diagnostic evaluation and treatment of critically ill patients in an intensive care unit (ICU) and during major surgical procedures. Ventricular performance is determined primarily by heart rate and cardiac contractility, preload and afterload.

The heart rate is measured easily from an electrocardiographic monitor. If diastolic filling is maintained constant, cardiac output will increase as heart rate increases. Myocardial contractility may be assessed indirectly by invasive or noninvasive methods, but a practical method for continuous monitoring of contractility is not yet available in clinical practice. Afterload is the myocardial wall tension developed during contraction and is proportional to arterial blood pressure. Therefore, it is easily assessed by conventional blood pressure monitoring.

The accurate assessment of preload, defined as myocardial fiber length at the end of diastole, presents a difficult problem. Preload is related to ventricular volume, and ventricular volume is, in turn, roughly proportional to left ventricular end-diastolic pressure (LVEDP). Although ventricular volume and LVEDP change in the same direction, the relationship is not linear in normal hearts and it is further altered by conditions which change myocardial compliance. Mean left atrial pressure (MLAP) is frequently used in the clinical setting to assess LVEDP since the two are nearly identical in patients with normal hearts, but MLAP is an inaccurate reflection of LVEDP in patients with abnormal left ventricular function, and it can only be measured by direct insertion of a catheter through the left atrial wall at operation.

The introduction of a balloon-tipped flow-directed pulmonary artery catheter made available an effective and reasonably safe clinical method for assessment of MLAP (and, therefore, indirectly, preload).

In its simplest form, the pulmonary artery catheter has two lumina. One extends the entire length of the catheter, opening at the tip, through which it is possible to measure pressure and collect blood samples. The other lumen opens just proximal to the catheter tip and is used to inflate the balloon. When the catheter is placed in a peripheral branch of a pulmonary artery, balloon inflation will obstruct arterial blood flow in that segment of the pulmonary arterial system. The pressure then recorded beyond the balloon is no longer pulmonary artery pressure but becomes the pressure transmitted retrograde from the left atrium. This pulmonary artery occluded pressure (PAOP) is essentially identical to pulmonary wedge pressure (PWP). A close relationship exists between MLAP and PWP when PWP is less than 25 mm of mercury. Measurement of PAOP consequently allows for a relatively accurate determination of MLAP which in turn corresponds to LVEDP. As LVEDP increases so does PAOP.

Modifications of the catheter include an additional lumen which opens into the right atrium, and a thermistor probe 10 cm proximal to the tip of the catheter, for measuring cardiac output by thermodilution. The versatility of the pulmonary artery catheter is notably increased by these two additions. For example, it is also possible utilizing body surface area, heart rate, cardiac output, mean arterial pressure, mean right atrial pressure and PAOP to calculate stroke volume index, total peripheral resistance, pulmonary vascular resistance, and left and right ventricular stroke work index.

Because of the disparity between central venous pressure and PAOP in patients with compromised left ventricular function, uncompensated cirrhosis, advanced peritonitis or multisystem trauma, catherization of the pulmonary artery is indicated for adequate monitoring of fluid therapy or a hemodynamic intervention in the ICU or during anesthesia. Other uses are in the management of patients during controlled hypotension and in monitoring massive volume replacement.

Premature ventricular contractions may occur during 17 percent of attempted catheter placements. The arrhythmias are transient, and usually

subside when the catheter tip is in the pulmonary artery. Symptomatic pulmonary infarction may result if the catheter floats into a permanent wedge position or the balloon is left inflated for a prolonged time. Thrombosis associated with the pulmonary artery catheter has been reported, as has perforation of the pulmonary artery and knotting about intracardiac structures. Balloon rupture may occur if it is overinflated, or if the catheter is reused. Sterile technique during insertion and manipulation of the catheter will minimize the risk of infection.

Despite its shortcomings and complications, the flotation pulmonary artery catheter is a safe and practical clinical device that provides reasonably accurate information about left ventricular function.

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Anesthetic Management for Patients with Coronary Artery Disease

THE MOST CHALLENGING and important problem facing an anesthesiologist caring for a patient with coronary artery disease is the control of factors affecting myocardial oxygen supply and demand.

The major controllable determinant of myocardial oxygen supply is the diastolic arterial blood pressure. Below a critical lower pressure limit, reduced flow across narrowed coronary arteries may cause a loss of autoregulation of coronary flow. Therefore, anesthetists must keep patients' diastolic blood pressure high enough to ensure adequate coronary blood flow. Although critical lower pressure limits vary from patient to patient, most anesthetists attempt to maintain the diastolic pressure above 50 mm of mercury. One should suspect a problem with low myocardial oxygen supply if changes in ST segments, arrhythmias or pump failure occur.

The four major determinants of myocardial oxygen demand are heart rate, afterload (the systolic blood pressure plus any aortic valve pressure gradient), preload and the state of myocardial contractility. The rate-pressure product (heart rate times systolic blood pressure) correlates well with myocardial oxygen demand. In the presence of an increasing rate-pressure product, changes in ST segments, arrhythmias or pump failure should lead an anesthetist to suspect that myocardial oxygen demand exceeds supply. In general, high myocardial oxygen demand is produced by patient anxiety, light anesthesia (especially during intubation), lack of β-adrenergic blockade, or the overuse of pressor or cardiotonic drugs.

Adequate monitoring of patients with coronary heart disease requires a continuous electrocardiogram on which ischemic ST-segment changes can be seen. If possible, lead V5 should be monitored, since it is usually the most sensitive in evaluating changes in the ST-segment. In the absence of V lead capabilities, lead 2 is the best second choice. Direct intraarterial blood pressure monitoring is recommended so that second-to-second changes can be observed, and in addition, arterial blood-gas determinations should be made. If the disease is severe or there is substantial left ventricular dysfunction (or both), a pulmonary artery catheter (Swan-Ganz) should be placed in order to continuously determine the left ventricular filling pressures (preload).

It is important to realize that there are two major categories of patients with coronary artery disease, requiring notably different management techniques. The first includes those patients with little or no myocardial damage, a normal cardiac reserve, no history of cardiac failure, a left ventricular end-diastolic pressure (LVEDP) under 14 mm of mercury, ejection fraction over 0.4 and no left ventricular aneurysm. These patients tend to have hyperdynamic responses to any stimulus (for example, anxiety or pain). Management should include adequate preoperative discussion and sedation, adequate anesthesia, β-adrenergic blockade both preoperatively and intraoperatively, the use of intravenously given nitroglycerine or sodium nitroprusside (or both), intratracheal spray with lidocaine before tracheal intubation and possibly, metocurine instead of pancuronium. The use of enflurane or halothane, either as the major anesthetic agent, or as an adjunct to a narcotic technique, is desirable. All of the above measures tend to minimize increases in myocardial oxygen demand.

The second patient category includes patients with previous major cardiac damage, including ventricular aneurysm, mitral or aortic valvular dysfunction, heart failure or previous myocardial infarction, an LVEDP over 14 mm of mercury, an

ejection fraction under 0.4 and, therefore, a compromised cardiac reserve. In these patients heart failure tends to develop easily if myocardial depressants are used. Therefore, propranolol, halogenated anesthetic agents and thiopental must be used cautiously, if at all.

It is essential, therefore, that patients receive a thorough preoperative evaluation, and be appropriately prepared for anesthesia. The plan of anesthetic management should have as its major goal the maximizing of myocardial oxygen supply, and minimizing of myocardial oxygen consumption.

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Protection of the Brain From Progressive Ischemia

INCREASING CAPABILITY in cardiopulmonary resuscitation both in and outside hospitals has resulted in a large number of patients whose cardiovascular and pulmonary systems are stable but who have sustained severe brain damage. As a result, a considerable interest in the concepts of cerebral resuscitation has developed. In the past, varying combinations of steroids, osmotic diuresis, hypothermia and hypocarbia have not ensured recovery without neurologic deficit following severe global ischemia.

Recent studies suggest that barbiturates may have a protective effect following both focal and global ischemia. Investigators at the University of Pittsburgh have shown there to be pronounced decreases in neurologic deficits when thiopental was administered to primates following 16 minutes of cerebral ischemia. In a preliminary pilot study at Stanford University Medical Center, four patients having sustained cardiac arrests with estimated global cerebral ischemia in excess of seven to ten minutes were given sodium thiopental in doses averaging 578 mg per kg of body weight over times ranging from 48 to 72 hours. Criteria for determination of dose were achievement of blood levels between 40 and 90 μg per ml and an isoelectric electroencephalogram for 72 hours. Two of the four patients made a complete neurologic recovery. Similar beneficial neurologic recovery has been shown recently in patients with Reye syndrome, and following near-drowning or severe head trauma.

Mechanisms of action cited for the apparent success of barbiturates following cerebral ischemia include decreased cerebral edema, decreased intracranial pressure, interference with the "no re-flow" phenomenon, scavenging free chemical radicals and decreased cerebral oxygen demand. Although it is far too premature to make definitive statements as to the efficacy of barbiturates as a protective treatment for cerebral ischemia, experimental and clinical results appear quite promising. A prospective randomized study now is necessary to prove the value of this regimen. The dismal neurologic results following cardiac arrest attest to the need for developing improved diagnostic, therapeutic and monitoring techniques in the management of cerebral ischemia.

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Malignant Hyperthermia: An Update

MALIGNANT HYPERTHERMIA (MH), first described by Denborough in 1960, is a pharmacogenetic abnormality transmitted as an autosomal dominant pattern with reduced penetrance and variable expressivity. It may be triggered by inhalational anesthetics or depolarizing muscle relaxants and presents clinically as a hypermetabolic state, primarily of the skeletal muscle. Early clinical symptoms are tachycardia, tachypnea, and a respiratory and metabolic acidosis. Muscular rigidity of the jaw or extremities may or may not occur in the syndrome. Profuse skin sweating and ventricular arrhythmias have also been commonly described, with an increase in body temperature appearing as a later sign. Not all cases of MH

develop intraoperatively; fever and acidosis have been noted to occur during the immediate postoperative period. In some instances, the rapidity and intensity of progressing symptoms can be greatly modified in an individual patient, leading to difficulties of diagnosis and treatment.

Because the site of defect and causes of MH are not well-understood, present therapeutic measures are mainly supportive. In addition to aggressive treatment of the initial symptoms, it is important to look for and avoid the development of late complications. Such events include consumption coagulopathy, renal failure, hyperkalemia and neurologic sequelae. Because the sarcoplasmic reticulum of skeletal muscle from MH-prone persons appears to be defective in calcium transport, drugs that may be of benefit are those that can lower myoplasmic calcium. A promising new therapeutic agent in this category of drugs is dantrolene sodium (Dantrium®). Dantrolene is a hydantoin derivative used at present in the treatment of chronic muscle spasticity. Its probable mechanism of action is the reduction of calcium release from storage sites within the muscle cell by interference of excitation-contraction coupling. Although the drug has been used successfully in MH-susceptible pigs to control the syndrome, its efficacy in MH-prone patients has yet to be proven. Studies are now in progress to determine the effect of both orally given dantrolene for prophylactic use and of intravenous administration of dantrolene for acute episodes of MH.

There is no single, specific diagnostic test for detection of susceptible persons or carriers. Creatine-phosphokinase levels (CPK) can sometimes be nonspecific and misleading. Furthermore, other disease states such as myopathies, osteogenesis imperfecta and hypothyroidism can result in elevated CPK levels. At present, the *in vitro* halothane contracture test on muscle biopsy specimens appears to be a more reliable indication of MH susceptibility. Conflicting laboratory results of this test in early literature have been attributed to a lack of standardization of procedure. Because false-negative results of CPK and of the contracture test can occur, it is now felt that a battery of tests would increase the certainty of diagnosis. Such tests should include determinations of serum inorganic pyrophosphate and CPK isoenzymes, muscle histochemistry and electronmicroscopy, and electromyography.

Until the pathogenesis of MH is elucidated, morbidity can be decreased only by the following measures: (1) careful preoperative questioning about family history; (2) maintaining a high index of suspicion when clinical features of hypermetabolism appear during anesthetic management and (3) applying immediate, aggressive measures of withdrawing the triggering agent or agents and of providing supportive therapy.

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General Anesthesia for Cesarean Section

FOR VARYING REASONS many cesarean sections are carried out under general anesthesia. While modern techniques have prolonged the period of anesthesia that will be tolerated by a fetus without producing significant depression, there still is much concern with minimizing the effects of the anesthetic. It has been shown that increased maternal oxygenation to an oxygen pressure of approximately 300 mm of mercury will measurably improve neonatal outcome. Earlier concern that maternal hyperoxia would lead to uterine artery constriction has been disproved and current belief is that at least 50 percent oxygen should be administered to the mother during cesarean section before delivery of the infant.

Although nitrous oxide has become the primary agent for maintenance of general anesthesia for cesarean section, because of its minimal depressant qualities, the amount of nitrous oxide should be limited to 50 percent. This has led to a rather large percentage of women who have some awareness during general anesthesia. This awareness may range from dreaming postoperatively to actually being able to repeat verbatim conversations that occurred during the operation. Fortunately there is seldom recollection of pain.

In order to minimize maternal awareness, and still maintain the advantages of increased oxygen administration most obstetric anesthesiologists have now taken to adding a small amount of a potent inhalation agent to a 50 percent nitrous oxide-oxygen mixture. For instance, one may use

0.5 percent halothane or 0.25 percent methoxyflurane. There has been some reluctance to use halogenated agents due to their known uterine relaxant properties and the resulting fear of increased blood loss. Findings in recent studies have shown that the addition of the previously mentioned concentrations does not affect blood loss during cesarean section. There is also concern that the potent agents may add to neonatal depression. Again, in the concentrations recommended for the few minutes before delivery there are data showing no greater incidence of fetal depression. As a matter of fact, there is an as yet unsubstantiated belief among some anesthesiologists that the fetus may actually be improved by the addition of a potent agent that decreases maternal catechol secretion and thereby improves uterine and placental blood flow. Maternal awareness certainly is decreased with the technique.

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Update on Mechanical Ventilation

THE RECENT INTRODUCTION of positive end-expiratory pressure (PEEP) and intermittent mandatory ventilation (IMV) of a spontaneously breathing patient, along with an increased understanding of the toxicity of unnecessarily high inspired concentrations of oxygen (FIO_2) have changed the clinical management of patients whose lungs are ventilated mechanically. The following describes current practice of mechanical ventilation, weaning and extubation.

As soon as the trachea of a critically ill patient is intubated, controlled mechanical ventilation is initiated with a tidal volume of 12 ml per kg of body weight, a respiratory rate of 10 to 12 breaths per minute and an FIO_2 of 1.0. PEEP is progressively added (range 0 to 20 mm of mercury) until the arterial partial pressure of oxygen (Pao_2) is 80 to 90 mm of mercury with an FIO_2 less than 0.5. Utilizing fiber-optic bronchoscopy, hourly turning of the patient, chest physical therapy, and frequent suctioning generally allows the physician to decrease PEEP to less than 10 mm of mercury with continued maintenance of an adequate Pao_2 with a low FIO_2. When PEEP is less than 10 mm of mercury, IMV is begun initially at 10 breaths per minute. The rapidity by which the IMV can be reduced is dictated by and is directly proportional to the patient's vital capacity (VC) and maximum inspiratory force (MIF). As the IMV rate is decreased, the patient is monitored by VC, MIF, the spontaneous respiratory rate (SRR) and arterial partial pressure of carbon dioxide ($Paco_2$). When Pao_2 equals 80 mm of mercury FIO_2 is less than 0.5, PEEP is 5 mm of mercury, VC is greater than 10 ml per kg of body weight, MIF is greater than −20 mm of mercury, IMV is less than or equal to 1, SRR is less than 20 per minute and $Paco_2$ is approximately 40 mm of mercury, then the x-ray film of the chest is critically examined. If the x-ray findings are reasonably equivalent to the premorbid x-ray findings, or are rapidly improving and no new changes have appeared (such as infiltrates or pneumothorax), the patient's trachea then is extubated and oxygen is administered via nasal prongs or plastic mask.

The logic of this approach is that first the patient's lungs function as an efficient gas exchange organ (FIO_2 less than 0.5, adequate Pao_2); second that the patient can sustain this gas exchange (adequate VC, MIF, SRR, $Paco_2$ on a low IMF); and third that no new complicating factor has occurred (adequate findings on an x-ray study of the chest).

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Recent Developments in Pediatric Anesthesia

THE PRINCIPLES governing pediatric anesthesia are those employed in adult anesthesia with the addition of special emphasis on fluid balance and temperature control. An infant in whom surgical operation is being carried out requires the greatest attention in these areas.

Preparation of the infant for operation demands that the operating room become a large isolette. The room is prewarmed to 25.6°C (78°F), a warming blanket is placed on the operating room table (not in direct skin contact), an infrared radiant heater is available and, whenever possible, anesthetic gases are humidified and warmed

to 32 to 35°C (89.6 to 95°F). This last measure may accomplish the desired goal of normal body temperature when the initial measures have been unsuccessful. Wash and irrigation solutions (including those used in cytoscopy) should be at body temperature, and the duration of exposure of peritoneal or pleural surfaces should be minimized. The transportation of ill neonates is a complex subject, but at the least requires the prevention of heat loss with the use of a transport isolette and, if necessary, wrapping the child in commercial packing bubble wrap plastic.

Intraoperative fluid management requires an understanding of renal physiology in the infant who is an obligate salt-loser. An infant should receive nothing by mouth within four hours of operation; fluid deficit before operation should then be calculated and replaced with 5 percent dextrose in 0.2 percent saline, 50 percent in the first hour and 10 to 25 percent per hour thereafter. "Third space" losses require replacement, and lactated Ringer solution with 5 percent dextrose is the fluid of choice. Replacement of blood loss is based on both the volume of loss and the hematocrit. Blood should be replaced when loss reaches 10 percent of estimated blood volume or to prevent the hematocrit reading from falling below 30 percent. Before this point, lactated Ringer solution with or without albumin may be used. Interestingly, humidification of inspired gases notably reduces insensible loss, and fluid administration rates require adjustment accordingly.

The actual choice of anesthetic technique is of far less importance than meticulous attention to detail, a knowledge of drug dosages (in mg per kg of body weight) and careful monitoring with stethoscope, temperature probe, electrocardiograms and blood pressure cuff.

Measurement of blood pressure with a Doppler device is preferred and should be used with the knowledge that a systolic blood pressure below 60 mm of mercury in a term infant, or below 45 mm of mercury in a premature infant, is abnormal.

Attention to the special points outlined in this review allows an anesthesiologist to provide an extension of the intensive care unit for the optimum care of an ill child.

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Metocurine—A 'New' Muscle Relaxant

ANESTHESIOLOGISTS have long sought a muscle relaxant with pure neuromuscular blocking properties, but no cardiovascular side effects. Such an agent could provide greater than usual stability during anesthesia, especially in critically ill patients. Recent attempts to synthesize such an agent have not been fruitful. However, there has been a revival in the use of an older drug, metocurine iodide (formerly known as dimethyltubocurarine iodide), which appears to have greater safety than agents presently in use. Originally synthesized in the 1930's, and overshadowed by *d*-tubocurarine (DTC), metocurine has seen little clinical use until the past several years.

Metocurine is classified as a nondepolarizing relaxant. The doses for 50 percent and 95 percent relaxation are 0.13 and 0.28 mg per kg of body weight, respectively. A dose of 0.3 to 0.4 mg per kg of body weight (25 to 30 mg in an average adult) produces satisfactory conditions for tracheal intubation. At this dose, metocurine produces the same neuromuscular effects as pancuronium, 0.1 mg per kg of body weight, or DTC, 0.6 mg per kg of body weight. Onset time for an intubation dose is approximately four minutes. For the *same* amount of paralysis, its duration is similar to either pancuronium or DTC. For use in maintenance of relaxation of intubated patients, a dose approximately half that of DTC, or four times that of pancuronium is necessary (2 mg of DTC is approximately equal to 1 mg of metocurine, and 1 mg of pancuronium is approximately equal to 4 mg of metocurine). In the absence of renal failure, metocurine is readily antagonized by neostigmine or pyridostigmine. As with other relaxants, the use of a nerve stimulator will aid anesthesiologists in selecting the optimum dosage and evaluating recovery from neuromuscular blockade.

Cardiovascular effects are less pronounced than those after administration of DTC or pancuronium. In approximately a fourth of patients a decrease in arterial blood pressure will occur, and also erythema of the skin (possibly from histamine release), but these changes are less pronounced than those seen after DTC administration. Hypertension does not occur, in contrast to pancuronium; and tachycardia, when occurring, is much less prominent than that from either pancuronium or gallamine. All cardiovascular changes can be

lessened by slow administration of the drug (over one to three minutes).

Metocurine seems to be the agent of choice for use in critically ill patients in whom tachycardia and hypertension of pancuronium or gallamine are to be avoided, or in whom the pronounced hypotensive effects of DTC may be detrimental. For example, patients with coronary artery disease, arterial hypertension, aortic insufficiency, mitral stenosis, mitral insufficiency or vascular aneurysms would seem to be good candidates for its use. Perhaps someday a pure neuromuscular blocking agent, without any cardiovascular side effects, will be available. Until that time, metocurine appears to be the agent with the least cardiovascular side effects of available relaxants.

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Is Fentanyl a Wonder Drug?

FENTANYL, a short acting (20 to 30 minutes) narcotic, was introduced in the United States in 1968 in combination with droperidol as Innovar®. Later it became available as fentanyl citrate (Sublimaze®) and now it is increasingly being used with nitrous oxide or other drugs for balanced anesthesia. Fentanyl is 100 times more potent and 10^7 times more lipid soluble than morphine. Its onset is rapid (seconds) and the serum rapid phase half time is two to three minutes. Fat tissue concentrations such as in brain rapidly exceed serum levels, and this gradient probably contributes to the slower serum elimination phase (half time one to four hours depending on dose). Urinary excretion of unaltered fentanyl only amounts to 20 percent of the injected drug. It is a weak base with a dissociation constant (pKa) of 7.4 to 7.5 (in methanol), and is highly bound (70 percent) to serum proteins. These characteristics indicate a kinetic similarity to thiopental. Unlike thiopental, fentanyl is an excellent analgesic but does not have good hypnotic or amnestic properties.

It is a clinical impression that compared with morphine, fentanyl has more autonomic nervous stimulation (bradycardia, gastrointestinal effects) and it may produce skeletal muscle hypertonicity which is related to rapid intravenous injection. In healthy patients fentanyl is free of significant cardiovascular side effects, and unlike most narcotics, fentanyl does not produce general vasodilation, but rather mild vasconstriction probably related to catecholamine release. Fentanyl, therefore, is useful for analgesia and anesthesia in cardiac and critically ill patients.

The main problem with fentanyl, however, is that measurable respiratory depression persists much longer than clinical analgesia. Residual respiratory effects may be seen four to six hours after a single dose. This may be related to the total amount of the drug given since small amounts (1 to 5 ml) are usually reversed easily, but larger amounts (over 10 ml) either have a cumulative effect or have a different mechanism of depressing the respiratory centers. It has been observed that naloxone may not completely reverse the respiratory effects following large doses. This respiratory side effect should be a strong caution to the occasional or inexperienced user of this increasingly popular potent drug.

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Recent Advances in the Management of Head Injured Patients

OSMOTIC DIURETICS, induced respiratory alkalosis and corticosteroids are the principal aids for decreasing an increased intracranial pressure following head injury. Mannitol is the osmotic diuretic most frequently employed for decreasing intracranial pressure. It effects water removal from normal brain rather than edematous tissue, and is usually given intravenously in a dose of 1.0 to 1.5 grams per kg of body weight. It begins to reduce intracranial pressure within 15 minutes, and its decompressive effects last for four to six hours. Repeated administration of mannitol can result in a hyperosmolar state and cause central nervous system dysfunction. However, it has been shown that smaller doses of mannitol (0.25 to 0.5 grams per kg of body weight) given every

three to four hours are effective in reducing intracranial pressure while avoiding the risks of hyperosmolarity. Finally, concomitant administration of furosemide can reduce the central venous pressure increase due to mannitol, as well as potentiate the therapeutic effect of the osmotic agent.

Hyperventilation can lower intracranial pressure within minutes. New information indicates that during long-term hyperventilation therapy (arterial carbon dioxide pressure approximately 25 mm of mercury), cerebral spinal fluid pH returns toward normal and may attenuate the cerebral vascular constriction induced by the reduction in arterial carbon dioxide tension. Under these circumstances a trial of more extreme hypocapnia may be indicated.

The effectiveness of steroids in the management of traumatic cerebral edema has been established, although in order to accomplish a reduction in the posttraumatic episodes of intracranial hypertension and improve overall survival rates, very large doses of dexamethosone are required. The dose schedule derived from two well-controlled studies in Germany indicates that 48 mg should be given intravenously immediately, followed by 8 mg every two hours for 48 hours, 4 mg every two hours over the next 48 hours, and finally 4 mg every four hours on days 5 through 8.

Recently barbiturates have been used as an adjunct to decrease intracranial pressure in patients with head injuries. Following the observations that thiopental could rapidly but transiently reduce intracranial pressure during anesthesia in neurosurgical patients, large doses of barbiturates were tried in patients with neurotrauma. Besides reducing intracranial hypertension, use of pentobarbital also lowered the daily dose of mannitol required to maintain intracranial pressure below 20 mm of mercury. The initial loading dose of pentobarbital is 3 to 5 mg per kg of body weight, and this is followed by maintenance doses of approximately 1.5 mg per kg of body weight given hourly with treatment usually continued for five days. A dose is withheld if the mean arterial blood pressure falls below 70 mm of mercury. This therapy, when included in the neuroresuscitative protocol outlined above, appears to improve the nonvegetative survival rate by 10 percent.

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EDITORIALS

Avicenna Revisited

Among the desperate needs of the underdeveloped countries, health care ranks high. Health care is here used in its broadest sense to include personal treatment for disease, preventive medicine (insofar as we understand that attractive phrase) and the innumerable variables that may be grouped as public health. In many countries it also includes birth control, as numbers press upon resources in marginal Malthusianism. The problems of health merge into the domains of sociology, economics, education and governance, and cannot be easily circumscribed by boundaries of disciplines or of countries. The World Health Organization was established for the simple reason that problems of health are common to all countries, although regional silhouettes of disease frequencies may vary greatly.

The United States has played an important but uneven role in international health. Individual persons, private institutions (notably the Rockefeller Foundation) and governmental agencies have assisted directly or have lent major support to international programs. The results of biomedical research have universal application, so that the National Institutes of Health are actually international in their relevancy. Also, the United States has become a Mecca for medical education, attracting many of the best young physicians from around the world into its postgraduate programs for clinical and research training. It is this latter phenomenon that has been ambiguous in its effect. We can be proud that many of the physicians and medical educators, and those in other health disciplines who hold positions of great responsibility in foreign countries, have received their educations in our institutions. We cannot be proud of the overwhelmingly positive balance in talent trade which has occurred as a by-product of this educational exchange. FMG (foreign medical graduate) is an abbreviation around which swirls a confused array of emotional and political forces, largely motivated by parochial considerations of what is perceived as best for American medicine. Less attention has been directed to the effect that this massive migration of trained professionals may have had on their respective countries of origin. The net immigration of foreign physicians seems likely to be sharply curtailed in the future due to changes in our immigration policy, the increasing competition from United States graduates for limited positions, and in some cases by restrictions on freedom of emigration of physicians by their respective countries. As an unfortunate by-product the forces which will reduce immigration also tend to limit access of foreign health professionals to the best in American postgraduate medical education. It is therefore imperative that developing countries look to their own resources for postgraduate education and research. Iran is a country that is attempting to make this transition.

Iran has a recorded history of 2,500 years. Its earliest university, the Jondi Chapour university, was founded 1,700 years ago during the Sassanid dynasty as a center of higher learning in medicine, philosophy and pharmacology. Avicenna (980 to 1037) was one of the distinguished physicians of antiquity. His *Canon of Medicine* was the forerunner of present textbooks of medicine and was widely used in Europe for centuries. During those centuries Persian education declined and as recently as 50 years ago there was no university in Iran. At present Iran shares many of the problems of developing nations in its health care. Some 40 percent of Iranian physicians live in Tehran, which contains 12 percent of the nation's population of 35,000,000. The great majority of other Iranian physicians live in the next five largest cities. There are now eight medical schools in Iran and seven more will be established within the next two years. The present number of graduates is about 700 annually, but this number will double within the next decade. Facilities for postgraduate education and biomedical research are notably limited. Pahlavi University Faculty of Medicine in Shiraz has had the strongest academic program in medicine and the medical sciences as judged by Western standards. A recent survey showed a net emigration of 50 percent of its graduates to the United States (two thirds came here for training and approximately two thirds of those remained permanently). It is estimated that more

than 3,000 Iranian physicians now live in the United States. Meanwhile many of Iran's problems in health care continue to be inadequately addressed.

Iran is more fortunate than most developing countries. In addition to its long cultural heritage, it now has the resources to undertake new initiatives in health care and health education. One such initiative is the establishment of the Imperial Medical Center of Iran (IMCI) now under construction in Tehran. A consortium of medical schools—Columbia, Cornell and Harvard—was involved in advising about the organization and development of this major academic health science center. An international Board of Governors, representing these and other American medical schools, continues to advise the Director, Abdol Hossein Samii, concerning academic policy. As presently projected the IMCI will undertake a number of activities more or less simultaneously. Its educational activities will include (1) a medical school with a strong science base tilted toward the training of academic physicians as well as practitioners, (2) a graduate school of biomedical sciences for the doctoral degree, (3) an undergraduate and graduate school of nursing, (4) a school for allied health professionals, (5) a school of health planning management and (6) a strong program for housestaff and specialty training. An important development has been the establishment of the Pahlavi Library of Medicine and Biomedical Communications Center, already operating in Tehran and linked to the National Library of Medicine via satellite. This library has been designated as the World Health Organization's regional library for the Middle East and Eastern Mediterranean region. An Institute of Continuing Education is being established which is of particular importance in a country with isolated facilities, comparatively poor communications and uneven levels of professional competency. The research programs envisioned at the IMCI will be in most of the traditional disciplines but there will be an attempt to give special emphasis to problems of special pertinence not only to Iran but to Third World nations in general: infectious disease, nutrition, population control, public health and health care delivery. The realization of these ambitious plans in the next few years should also establish the IMCI as a center for tertiary care in Iran and the Near East.

Is this a wise investment of Iranian resources? Certainly it would not be so if the building of a model academic center in Tehran were the only major investment made by the government to improve the health care of the Iranian people. The problems that must be faced in providing health care in Iran are multiple and complex. The IMCI will help solve some, but by no means all of them. IMCI will succeed only to the extent that it is a resource for training and research to meet the pressing problems of improving the quality of and the access to health care in Iran. It will be one important component of a solution and as such deserves the attention and assistance of American medicine. As this talented and ambitious people develop their own resources in health care, other nations may benefit on regional and international levels as well. They did so in the time of Avicenna. Why not now again 1,000 years later?

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Associate Editor

Trends in the Science and the Art

THERE ARE SIGNS that we may be approaching a need for some change in medical practice as we have known it in the last few decades. On the one hand physicians have increasingly held to the premise that everything that is important in patient care must have a scientific basis, and if it does not it is not important. On the other hand a growing segment of the public, and many professionals and would-be professionals, are becoming dissatisfied with the care they are receiving at the hands of scientific doctors and are seeking care, even relief, elsewhere. Scientific medicine is sought and given its due when there is something that can be fixed, but often, perhaps even more often, there is a void of need which scientific medicine does not fill, and indeed may never be able to fill.

One senses two distinct social trends. One is to reduce or eliminate what is not scientific in patient care. The other is a growing search for and acceptance of alternative methods of care which may or may not have any scientific basis. The first trend seems motivated both by a laudable desire to rid scientific patient care of its impurities and possibly also by a desire to control costs. Donald Kennedy, Commissioner of the Food and Drug Administration, is in the forefront of this trend having recently said "No drug should be

permitted on the market unless it can be proved by rigorous experiment to alter the course of some ailment or disease; that is, it must be effective."[1] And one can easily see, the cost squeeze being what it is, that this approach may soon be applied to just about anything and everything doctors do for their patients. Not only drugs but services and procedures, whether in office, hospitals or elsewhere, may be subjected to the same test of scientific proof of effectiveness—and this is likely to be persuasive.

This writer is troubled by so rigorous a scientific approach. On the one hand as physician scientists we instinctively support this position. It will go against the scientific grain to justify the use of a pill, or a service, or a procedure unless we can show that it is effective. But there is a gnawing feeling that there is something wrong here. Putting aside the obvious question of whether we know enough yet to require scientific proof of the effectiveness of everything we do in patient care, there seems to be something else important which has been left out. Perhaps there is a clue in the second trend, the trend to seek and accept alternative methods of care, which in many cases seems to be almost a revolt against scientific medicine. Somehow, scientific medicine as we practice it today does not seem to satisfy patients and the public as well as did the old time "horse and buggy" doctor of the prescientific era. Clearly medicine is losing something, or has lost it.

This something we are losing or have lost is obviously not science. We have more and better science than ever. If it is not science, then it must be what used to be called the art, but which now seems to lack definition or description, or even much genuine interest. Experienced clinicians know what this something is, and patients and the public seem to sense it. And in the present stage of our knowledge and understanding it is not something that can be proved effective or not effective by rigorous experiment. We will need to have far more knowledge in the social and behavioral sciences and a much better comprehension of the human environment before this can be done. What seems really needed is much more emphasis on the teaching and practice of the art, in the face of professional preoccupation with the science and public preoccupation with feeling better in a tense, stressful and far too polluted world—with which many people find it difficult to cope.

There is danger now that the regulatory authorities in their frantic need to curtail costs, will, by seeking proof of effectiveness by rigorous experiment or otherwise, unwittingly deprive physicians of some essential tools of the art which they should probably be using more, not less. These tools are medicines that do no harm and the services of caring and concern, in addition to those of curing. In a sense medicine may be approaching an intersection in the road just ahead, where it may continue on what is still the relatively undeveloped country road of medical science, or rejoin the highway, where most of the traffic is, by once again embracing the whole of patient care—that is, care of the whole patient. In our present state of knowledge, medicine is without question still an art as well as a science, and the time has come when this needs more than just lip service. If we are to do this, the strict scientific approach must be leavened with a recognition that it will be a long time, if ever, before everything in patient care can meet the standard of scientific proof by rigorous experiment.

—MSMW

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EDITORIAL REVIEW

Progress With Hepatitis B Virus

Recent research with hepatitis B virus (HBV) emphasizes that this is a unique virus in several interesting ways; and as in all research, experimental results have continued to raise many new questions as old questions are answered. Gitnick's review in this issue covers some of the new ground and here I will only point out several of the unanswered questions about the nature and behavior of this important virus. One question concerns the identity of the infectious form of the virus. The failure so far to infect tissue culture cells or convenient experimental animals has prevented development of assays for infectious HBV short of transmission to man or the few other susceptible higher primates such as chimpanzees. The current methods for infectivity testing are so cumbersome that it has not yet been possible to directly identify the infectious particle. However, one form of

hepatitis B surface antigen (HB_sAg) found in the blood, the Dane particle, has several properties suggesting that it may be the infectious particle: (1) its surface antigen (HB_sAg) appears to react with antibody (anti-HB_s) shown to protect patients against HBV infection,[1] (2) it contains a unique internal core antigen (HB_cAg) which is probably virus specified,[2] (3) its size[3] is consistent with estimates of the size of infectious HBV determined by ultrafiltration,[4] (4) its concentration in most sera[5] is consistent with titrations of infectivity in serum,[6] (5) its concentration in sera appears to correlate with the probability that patients will transmit infection to contacts,[7,8] (6) purified and concentrated preparations of Dane particles have been shown to be infectious at higher dilutions than previously shown for unfractionated HB_sAg positive serum,[9] (7) it is the only viral antigen form known to contain nucleic acid[10] and (8) deoxyribonucleic acid (DNA) reassociation experiments have shown that Dane particle DNA base sequences are only present in the DNA and ribonucleic acid (RNA) of infected liver and not in uninfected liver, and these sequences appear to be covalently attached to high molecular weight DNA[11] as are other viral DNA's when integrated into chromosomal DNA.

If Dane particles are hepatitis B virions, their ultrastructure, antigenc composition and other properties indicate that HBV is not a member of any known group of viruses but is a unique virus, and its structure is more complex than that of many simple viruses. Among the unique properties are the size and structure of the small circular DNA within the core of Dane particles and the presence of a DNA polymerase in the core.[10] The circular DNA molecule is double stranded over approximately two thirds of its length and the remainder is single stranded.[12,13] The DNA polymerase reaction closes the single stranded gap to make fully elongated double stranded circular DNA molecules of 3,200 nucleotide pairs. This is smaller than the double stranded DNA found in any other virus and such a molecule could specify no more than three or four average sized proteins. Its small size raises a question of whether a single Dane particle DNA molecule could contain the entire genome of a virus with a structurc as complex as that of the Dane particle. The answer to this question must remain until the number and sizes of the HBV genes (or gene products) is known. The function of the single stranded region in this DNA molecule and the utility of the DNA polymerase for HBV are not known and remain central questions for understanding how this virus replicates and interacts with infected cells. No other viruses possess these interesting features.

Another important question concerns the relationship of the complex of antigens referred to collectively as "e" antigens or HB_eAg to HBV. These antigens are physically and antigenically distinct from HB_sAg and HB_cAg particles. Whether HB_eAg is an HBV gene product is not settled, although its occurrence exclusively in HB_sAg positive sera[6] and the frequent antibody response to HB_eAg following HBV infection are most consistent with this possibility. HB_eAg has proven difficult to purify so that it has not been well characterized chemically. An intriguing feature of HB_eAg is its common occurrence in sera of chronic HB_sAg carriers with high concentrations of Dane particles[7,8] and therefore its presence correlates (as do Dane particles) with a propensity for transmission of HBV infection from chronic carrier mothers to newborns[7] and from carriers to contacts accidentally inoculated with contaminated needles.[8]

Their regular occurrence together suggests that HB_eAg and Dane particles (and HBV) may be related in some direct way. It has been reported that anti-HB_e reacts with the surface of Dane particles[15] suggesting that HB_eAg may be a surface component of Dane particles. However, the antiserum used in that study was not proved to be monospecific and other investigators have failed to confirm that finding. It seems more likely that if HB_eAg is a component of Dane particles it is an internal component, although it is known to be distinct from HB_cAg. The question of its physical relationship to Dane particles remains unsettled.

Recently, Neurath and Strick[16] have reported that HB_eAg has properties similar to those of immunoglobulin IgG4 and have proposed that HB_eAg is an antibody formed in response to HBV infection and which possesses idiotypic antigenic determinants to which anti-HB_e is directed. If this hypothesis is correct, HB_eAg would not represent HBV specified polypeptide. Attempts to confirm the hypothesis have led others to the conclusion that HB_eAg is probably not an immunoglobulin and morc work will be required to cstablish or refute the hypothesis.

Another recent report[17] suggests than anti-HB_e inhibits lactic dehydrogenase (LDH) activity by

complexing with the enzyme in serum, raising the possibility that HB_eAg is a host component or exists as a complex with LDH in serum. This report is yet to be confirmed by others. The widely different findings concerning HB_eAg in the studies cited above emphasize the difficulties encountered with investigation of HB_eAg. Although the nature of HB_eAg remains unclear, its presence (like that of Dane particles) in serum may be clinically useful for identifying patients with a high probability of infectiousness for contacts and possibly those with underlying liver disease.

Clearly one of the most fascinating biological features of HBV is the relatively common occurrence of persistent infection in which virus forms circulate in the blood in very high concentrations often for many years. HBV persistence contrasts sharply with other persistent infections of man such as those with herpes viruses in which continuous viremia is not present and periods of inapparent or latent infection predominate. Continuous viremia does occur during persistent infection with certain other animal viruses, however. The closest parallel appears to be some persistent infections with oncorna viruses such as avian and murine leukemia viruses (ALV and MLV), other retroviruses such as equine infectious anemia virus (EIAV) and arena viruses such as lymphocytic choriomeningitis virus (LCM) in mice. In contrast to HBV, all are RNA viruses. A striking difference with the other viruses would appear to be that the predominant viral form in the blood in persistent HBV infection is incomplete virus in the form of particles of virus coat antigen (HB_sAg) and in the case of the other viruses numerous incomplete viral forms have not been observed. The biological significance of the defective virus forms in HBV infection is not clear. No defective forms with the properties of the defective-interfering or DI particles (that is, containing viral nucleic acid with deletions) found with almost all well studied viruses[18] have been recognized in the case of HBV. The potential relevance of DI particles for persistent HBV infection is that they play a role in maintaining persistent infections in some model systems with other viruses.[19]

The medical importance of persistent HBV infection is that it represents a source of virus for transmission from patients to their contacts and for perpetuation of this virus which has no known animal reservoir, and because of associated hepatic and extrahepatic diseases. In certain underdeveloped areas where HB_sAg carrier rates may exceed 5 percent or 10 percent of the population, neonatal transmission from persistently infected mothers may be a particularly important mode of virus transmission. Persistent viremia would also appear to be a favorable condition for transmission by blood feeding insects such as mosquitos. Although some populations of mosquitos have been shown to contain HB_sAg,[20] no direct evidence of transmission to man by mosquito vectors has been reported and this possibility deserves investigation.

One important question about HBV infections is the mechanisms which permit infection to persist indefinitely in many cases. In the case of ALV[21,22] and LCM[23,24] which do not appear to be cytopathic for their hosts, infection at very young ages and immunosuppression have been shown to favor persistent infection without associated disease. Evidence suggests that persistence in these cases results from a relative or partial immunological tolerance to the virus.[21-24] Disease associated with persistence of these viruses under some conditions is related to the immune response to the virus and not a direct cytopathic effect of the virus.[25] Very young age, immunosuppressing chemotherapy and diseases such as chronic lymphocytic leukemia, Down syndrome and lepromatous leprosy appear to be associated with an increased incidence of virus persistence after HBV infection. In addition, low infecting doses of HBV have been shown to result in long incubation periods, mild initial disease and frequent persistent infection.[26] A common denominator leading to persistent infection could be a modified or inadequate immune response to HBV under each of these conditions and this possibility must be investigated. Frequent persistent infection in the absence of liver disease suggests that HBV is probably not cytopathic for hepatocytes.

A wide spectrum of hepatic and extrahepatic disease may, however, be associated with persistent HBV infections. Polyarteritis,[27] glomerulonephritis,[28] infantile papular acrodermatitis,[29] cryoglobulinemia[30] and polymyalgia rheumatica[31] have been described in association with persistent HBV infection. The findings in well studied cases of extrahepatic disease are consistent with tissue damage mediated by HB_sAg immune complex deposition. Further study is needed to clarify the pathogenesis of these syndromes and if HB_sAg-

antibody complexes prove to be necessary for disease, the process should in theory be controlled by suppression of HB_sAg formation.

The pathogenesis of hepatic diseases such as chronic active hepatitis (CAH) and chronic persistent hepatitis (CPH) associated with persistent HBV infection is not as clear. Immune cell mediated tissue injury is a likely mechanism although direct evidence supporting this possibility is not abundant. An unexplained association in persistent HBV infections is the more frequent occurrence of Dane particles and HB_eAg in patients with hepatic disease compared with patients without disease.[14,32] The role these factors play in hepatic disease requires further study including assessment of the cellular immune response to HB_eAg and the antigen unique to Dane particles, HB_cAg.

Epidemiologic data are consistent with HBV having a central role in hepatocellular carcinoma in areas of the world where persistent HBV infection is common.[33] A direct role of the virus in carcinogenesis can only be proven by studies of the relationship of the virus and the tumor cell, tests of the ability of the virus to transform cells and studies of the effect of virus control program (for example, by vaccination) on the occurrence of this tumor in high-risk populations.

A final area of research where questions remain concerns methods for treatment and prevention of HBV infection. By far the most effective approach for control of HBV so far has come from the ability to use HB_sAg to identify infected patients and prevent transmission of virus by blood transfusion and other routes. The effectiveness of hyperimmune anti-HB_s in preventing infection is not completely clear because it has been compared with immune globulin containing anti-HB_s in prospective trials (such as Grady's study[34]) rather than with inert placebo. Because some trials (although not all) suggested effectiveness and its use was subsequently recommended, a prospective comparison with a true placebo is not now feasible and the degree of its effectiveness may never be thoroughly determined.

Vaccine development is well underway. Initial studies using purified HB_sAg particles in chimpanzees suggest that protection can be achieved.[1] Trials of this vaccine in man are underway. If it proves to be safe and effective in man, a vaccine could be useful for protection of certain high-risk populations.

Attempts to favorably affect the course of acute and chronic hepatitis B with hyperimmune anti-HB_s, transfer factor and some antiviral drugs have been unsuccessful. Two antiviral substances, however, have recently been shown to inhibit production of Dane particles in persistently infected patients. Human leukocyte interferon[35] and adenine arabinoside (ara-A)[36] have been shown to rapidly inhibit Dane particle production in all patients treated. Extension of the studies by these investigators to additional patients has shown the effect to be permanent in some patients and reversible in others. HB_sAg titers have irreversibly fallen in some patients during and following treatment. All evidence of virus infection in liver and blood cleared during interferon treatment of two female patients who have remained free of infection since treatment ended. Although these results are encouraging, only further studies including prospective controlled trials will determine the frequency and extent of the effects of such treatment.

HBV continues to be an important pathogen for man and interesting questions about its unique biology as well as the clinical challenge of its control remain.

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Newborn Infants With Congenital Heart Disease

WITHIN the past decade the attention of pediatric cardiologists and cardiovascular surgeons has shifted increasingly toward early infancy. Robert Gross' first patients, operated upon for patent ductus arteriosus 40 years ago, were school age children, and the first edition of Helen Taussig's book, published 30 years ago, advised cardiologists to postpone shunt operations, whenever possible, to beyond two years of age. By contrast, according to data from the New England Regional Infant Cardiac Program (NERICP), 28 percent of infants with cardiac problems admitted to a center between 1968 and 1974 were less than 2 days old and 29 percent of those operated upon were less than a week old.

The reason for this shift in emphasis from children and adolescents to infants and newborns is, first of all, the recognition that the vast majority of those who die within the first two decades with congenital heart disease will do so within the first year of life—actually within the first three months of life. The advances in surgical skills and diagnostic techniques represent the means through which pediatric cardiac surgeons and their cardiologist colleagues can respond to the challenge of high mortality in the very young. Furthermore, improved case finding, resulting from efforts at regionalization of neonatology as well as pediatric cardiology, allows more babies, at younger and younger ages, to reach cardiac centers. Finally, and the effect of economics on these matters should not be underestimated, the backlog of common congenital malformations in children and adolescents having been cleared up, cardiologists and cardiac surgeons are looking for new fields to conquer.

Since, for a variety of reasons, pediatric cardiology has become infant or even neonatal cardiology, the specialty conference this month by Kirkpatrick and co-workers on the differential diagnosis of congenital heart disease in the newborn is timely. Although the discussion of this complex problem is clear, concise and generally helpful, a few comments on the specifics may be indicated.

As to the five cardinal findings of significant heart disease, the writer of this editorial believes that tachypnea and cyanosis should be emphasized first and foremost as indicators of critical heart disease in infancy. Murmurs, by themselves, are in most instances of secondary importance. It is well to emphasize that some of the sickest infants with heart disease may have no murmurs at all (transposition of the great arteries, total anomalous venous return, and so forth) and some of the loudest murmurs may represent trivial malformations (small ventricular septal defect, minimal pulmonic stenosis). Acute congestive heart failure is most commonly manifested by tachypnea in newborns, whereas the more chronic failure, in late infancy, may be characterized by severe failure to thrive. Peripheral edema almost never occurs in the very young, except rarely with coarctation of the aorta. Hepatomegaly, as well as gallop rhythm, are ancillary evidences of congestive heart failure; the clinical diagnosis is based primarily on the findings of tachypnea not explained by pulmonary disease and significant car-

diomegaly in a radiogram. Strict reliance on the minutiae of cardiothoracic ratios in the newborn should be discouraged.

In the differential diagnosis of cyanosis the use of 100 percent oxygen, to exclude primary pulmonary disease, is important. One has to recognize, however, that frequently the results are inconclusive—that is, an oxygen pressure between 80 and 120 mm of mercury. The matter of differential cyanosis is a controversial issue: rarely is the line of demarcation very clear in newborns with a patent ductus arteriosus and coarctation, and often the phenomenon is noticed in perfectly normal newborns with a prolonged transitional circulation.

In regard to radiographic findings, it might be worth reemphasizing that newborns with transposition and intact ventricular septum, more often than not, have normal sized and normal shaped hearts. It should also be remembered that the right ventricular contour, the boot shaped heart, so typical of tetralogy of Fallot in children, may be a normal variant in a neonate.

There should not be any argument that left axis deviation and left ventricular hypertrophy are abnormal in young infants, but the quantitation of right ventricular hypertrophy in this age group in terms of normal or abnormal degrees may be difficult. Pure R waves in the right chest leads are suspicious at any time, as are upright T waves in these leads beyond the first week of life.

Within the past five years ultrasonography, M mode, two dimensional, with or without contrast, has become almost the most important tool in the early clinical recognition of congenital heart disease. Skilled echocardiographers can determine, with increasing precision, the number, position and functional state of A-V and semilunar valves, as well as the status of the atrial and ventricular septa, and infer the presence of a sizable patent ductus arteriosus.

We would then applaud the purpose of the specialty conference: emphasizing the importance of early recognition of critical congenital heart disease in infancy. We would also agree with the general principles suggested. In our own daily practice we would assume that all newborns with cyanosis or tachypnea not otherwise explained should be suspected of having severe congenital heart disease and should be referred promptly to a sophisticated cardiac unit for anatomic and physiologic diagnosis as well as early surgical operation. The principal differential diagnostic problem, excluding primary pulmonary disease, may not be solvable without cardiac catheterization studies. The fact that in around 5 percent of 2,378 infants with presumably critical congenital heart disease in the NERICP no structural heart disease could be shown at catheterization with angiography, is taken as evidence that there are limits to noninvasive diagnosis. Our own philosophy is to accept this figure as the price we have to pay not to miss the occasional total anomalous venous return, or even a silent patent ductus arteriosus, and is further justified by the relatively low risk of cardiac catheterization in skillful hands.

We would recommend very speedy action by pediatricians and neonatologists in pursuing the suspicion of critical congenital heart disease in the newborn, suggested by persistent cyanosis or tachypnea (or both). Asymptomatic babies with murmurs, and questionable findings on electrocardiograms (ECG) and x-ray films of the chest, may be investigated at a more leisurely pace. The most important diagnostic tools, in addition to careful history and physical examination, are the chest films and echograms obtained, and interpreted, by experts in pediatric echocardiography. An ECG, in the absence of obvious arrhythmias or tachycardias, is perhaps less sensitive in this situation.

One cannot emphasize strongly enough the necessity of emergency referral to a cardiac center with ample cardiac experience in newborns, for cardiac catheterization and possible surgical treatment, of all infants with reasonable suspicion of critical congenital heart disease. Neither the time of the day, nor weekends, nor the ego of a pediatrician aiming at a sensational diagnosis, should stand in the way of speedy referral. There is too much at stake.

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CASE REPORTS

Refer to: Baraff LJ, Hafkin B, Wehrle PF, et al: Human rabies. West J. Med 128:159-164, Feb 1978

Human Rabies

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HUMAN RABIES ENCEPHALITIS seldom occurs in the United States, and usually results from encounters with infected wildlife or exposure to rabid dogs outside this country. Reports of two survivors of presumptive human rabies have encouraged more intensive supportive care of recent rabies cases.[1,2] Successful management depends on rapid laboratory diagnosis and familiarity with the associated clinical problems. A recently described technique, immunofluorescence microscopy of skin biopsy material, may provide laboratory confirmation early in the clinical course, even before the development of rabies antibodies.[3] The risk of secondary cases among intimate contacts and hospital personnel is unknown, but has been assumed to be minimal. Guidelines should be defined for the isolation of patients with rabies, and indications established for postexposure prophylaxis for contacts of human cases.

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Submitted February 22, 1977.

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Report of a Case

On August 1, 1975, lower abdominal pain and dysuria developed in a 16-year-old Mexican girl, previously in good health. Ten days later fever, chills, frontal headache, difficulty in swallowing food and water, and a burning sensation on the plantar aspect of the left foot developed. Eight months previously, she had come to Los Angeles from Puebla, Mexico. She said she had not been bitten by any animals, including dogs or bats.

On August 13, 1975 the third day of significant clinical illness, she reported to the Pediatric Outpatient Department of the Los Angeles County-University of Southern California Medical Center. Her temperature was 36.8°C (98.2°F), and left costovertebral angle, left plantar and left popliteal tenderness were noted. There was no swelling, warmth, erythema, bruising, or evidence of trauma or animal bite on the left foot or in the left popliteal fossa. The remainder of the examination gave normal findings. Analysis of urine showed a specific gravity of 1.028, trace protein, 2+ ketone bodies, 2 to 12 leukocytes per high-power field, occasional red blood cells per high-power field and 2+ bacteria. A urine culture was done and the patient was given ampicillin with instructions to return in 24 hours.

She returned the following day, having been unable to take medication orally, or food or water, and was admitted to hospital for further observation. She complained of dizziness, a fear of dying and hearing voices, and was reportedly unable to recognize her parents at intervals. The dysuria and lower abdominal pain were unchanged. At this time her temperature was 38.8°C (101.8°F); pulse rate, 120 per minute; respirations, 24 per minute, and blood pressure, 160/100 mm of mercury. It was noted that her height was 145 cm and weight was 47 kg. She was oriented and talkative. The only abnormal physical findings were a grade I/VI systolic ejection murmur at the lower left sternal border, and left lower

quadrant abdominal and left costovertebral-angle tenderness. Findings on neurologic examination were unremarkable. Repeat analysis of urine showed 3+ protein, 5 to 10 leukocytes per high-power field, many red blood cells per high-power field and 4+ bacteria. Hemoglobin was 15.7 grams per 100 ml; leukocyte count, 15,500 with 88 percent neutrophils, 10 percent lymphocytes and 2 percent monocytes; erythrocyte sedimentation rate, 21 mm per hour; reticulocyte count, 1.8 percent. No abnormalities were seen on an x-ray film of the chest.

A nurse observed that "while being given sips of water the patient retches violently, spits up, breathes rapidly, becomes giggly, hyperventilates, and grabs her chair or another person for support." She was afraid to wash her hands and became excited when water from the intravenous tubing splashed her. However, during the night the patient became less excitable and was able to take sips of water with encouragement, swallowing her medication with some choking.

On August 16, the sixth day of her illness, deep tendon reflexes were noted to be hypoactive and the patient seemed more confused. The previous urine culture was reported as negative. A lumbar puncture showed an opening pressure of 170 mm of water, and closing pressure of 130 mm of water. The cell count was 14 leukocytes per cu mm, 9 polymorphonuclear neutrophils and 5 monocytes, with no red blood cells. The glucose value was 95 mg per 100 ml, the protein level was 26 mg per 100 ml and the chloride value was 117 mEq per liter. Gram stain was negative. That night anisocoria was first noted, left greater than right, and ankle jerks were no longer present.

On the seventh day of illness, the patient's neurological condition evolved rapidly. She was alternately lethargic and agitated. All deep tendon reflexes were absent, but she did withdraw from painful stimuli and move all extremities. Arterial blood gas studies showed an oxygen pressure of 56.9 mm of mercury; a carbon dioxide pressure, 21.3 mm of mercury, and pH, 7.47. That evening the patient was intubated when irregular respirations with increasingly frequent periods of apnea were noted. Several hours later she no longer withdrew from painful stimuli, although adventitious movements continued.

By the eighth day of illness, she was unresponsive to deep pain or verbal command and on examination a complete flaccid paralysis and aerophobia were noted. An electroencephalogram showed diffuse 2 to 3 and 6 to 7 per second slowing with no focal lesions. At this time the primary diagnosis was viral encephalitis and despite the negative history of animal exposure, rabies was strongly considered. Corneal touch preparations were negative by fluorescent rabies antibody technique (FRA).

On the tenth day of illness, a tracheostomy was carried out and a posterior nuchal skin biopsy specimen was obtained for FRA staining and was subsequently positive. On the 12th day a brief tonic-clonic seizure of the upper extremities and facial muscles occurred. The following day blood pressure gradually fell to 80/40 mm of mercury. The pupils of the eyes were noted to be irregular but responsive.

On the 14th day, findings on physical examination and x-ray study of the chest were compatible with left lower lobe pneumonia, and a Gram stain of tracheal secretions showed the presence of many polymorphonuclear leukocytes and Gram-positive diplococci. Intravenous administration of methicillin was begun. The pupils were noted to be 7 mm and nonreactive. On day 15, blood pressure fell abruptly to 50/30 mm of mercury and the heart rate fell to 40 beats per minute. An electrocardiogram showed a junctional rhythm. An isoproterenol infusion was successful in returning the blood pressure and heart rate to normal after therapy with atropine was inadequate. On the 16th day of illness the corneal, gag and caloric reflexes were negative for the first time. An electrocardiogram showed complete atrioventricular (A-V) dissociation; and cardiac arrythmias, including a 2 to 1 A-V block and junctional rhythms, occurred throughout the remainder of the clinical course.

That evening, for the first time, examination of the optic discs and a repeat lumbar puncture showed evidence of increased intracranial pressure; the opening pressure was 340 mm of water. The next day, a number 7 Fisher catheter was placed in the right cerebral ventricle to monitor intracranial pressure. At this time intraventricular pressure was 30 mm of water. Five cc of air was introduced, and x-ray films showed ventricular size to be normal. Hours later, the temperature fell to less than 35°C (95°F) and warming measures were instituted. The hypothermia, hypotension and areflexia persisted. On the 19th day, urine output increased to 200 to 300 ml per hour with a specific gravity of 1.003. The central venous pressure fell to zero and the serum sodium value,

previously normal, rose to 167 mEq per liter. Aqueous pitressin administration was begun for a diagnosis of diabetes insipidus.

On August 30, day 20, at 05:05 hours, the patient became cyanotic and asystolic. Cardiopulmonary resuscitation was successful. Three subsequent cardiac arrests occurred, and the final effort at cardiac resuscitation was unsuccessful.

Additional History

After the results of the rabies antibody titers, viral cultures and immunofluorescence tests were known, a comprehensive inquiry into this patient's history was undertaken. Eight months before admission she had lived in Coatzengo, a small village in the state of Puebla, Mexico. There, the family owned five dogs, including three puppies. One of these puppies was believed to have bitten the patient and ten other family members during August and September 1974, and then disappeared. In November 1974 an older female dog, the mother of the puppy, became ill, with decreased appetite and activity, and died in a few days. In Puebla state, rabies is highly endemic; in 1975 there were 280 cases of animal rabies, including 130 in dogs, confirmed in the state. The patient's parents and family did not accept the diagnosis of rabies and refused rabies prophylaxis.

Postmortem Examination

The following pertinent abnormalities were present on postmortem examination:

The brain weighed 1,325 grams. It was extremely soft and had lost its normal configuration. The sulci were deep and the convolutions prominent. Microscopic evaluation showed pronounced edema and severe anoxic changes. There were small foci of hemorrhage. In a few fields there were localized collections of mononuclear and polymorphonuclear cells surrounding small blood vessels. There was no supportive inflammatory process.

The heart was grossly normal. The myocardial fibers were large and pale staining, and there was

TABLE 1.—*Virology Results**

	Virology Culture† and FRA Tests		*Rabies Antibody Titers*		
Date	*Specimen*	*Result*	*Specimen*	*IFA*	*FFIT*
8-18 . .	Rectal swab	Negative	. .	. .	. .
8-18 . .	Nasal swab	Rabies pos.	. .	. .	. .
8-18 . .	Corneal touch prep‡	FRA neg.	. .	. .	. .
8-19 . .	Corneal touch prep‡	FRA neg.	. .	. .	. .
8-20 . .	Skin biopsy§	FRA pos.	Serum	<1:4	1:16
8-21 . . .		. .	Serum	<1:4	1:64
8-22 . .	Saliva × 2	Rabies pos.	Saliva	<1:4	<1:4
8-22 . .	Pharyngeal swab	Rabies pos. Herpes type 1	Serum	1:16	1:512
8-22 . .	Rectal swab	Negative	. .	. .	. .
8-25	¶	. .	Serum	1:256	>1:16384
8-26 . . .		. .	Serum	1:2048	1:8192
8-27 . .	Sputum	Negative	Sputum	1:48	>1:768
8-27 . .	Urine	Negative	. .	. .	. .
8-28 . . .		. .	Plasma	1:4096	. .
8-28 . . .		. .	CSF	1:10	1:40
8-29 . . .		. .	Serum	1:2048	1:16384
8-31 . .	Brain (parietal cortex)	Rabies pos. FRA pos.	Serum Brain (1:8)	1:2048 1:32	1:8192 1:64

CF = complement fixation
CSF = cerebrospinal fluid
FFIT = fluorescent foci inhibition test for neutralizing antibody
FRA = fluorescent rabies antibody
IFA = indirect fluorescent antibody
SLE = St. Louis encephalitis
VEE = Venezuelan equine encephalitis
WEE = western equine encephalomyelitis

*Done by the Viral and Rickettsial Disease Laboratory, California State Department of Health.

†Using suckling mice, primary monkey kidney cells, and human fetal diploid lung (HFDL) cells; rabies virus isolates were in mice; herpes virus isolate was in HFDL cells.

‡Done by the Los Angeles County Division of Laboratories.

§Done by Dr. Donald Blendon, University of Missouri.

¶Herpes IFA 1:16, CF test for SLE, WEE, VEE <1:8.

interstitial edema of heart muscle and localized collections of lymphocytes, notably about small nerve fibers in the myocardium.

Virology Results

The results of all viral cultures, fluorescent rabies antibody (FRA) tests and antibody determinations are listed in Table 1. Corneal touch preparations, obtained on the eighth and ninth days of clinical illness, were negative for rabies virus by the FRA technique, but a skin biopsy specimen obtained on the tenth day of illness from the posterior nuchal region showed parafollicular fluorescence when stained with fluorescein conjugated rabies antibody. Rabies virus was subsequently cultured from saliva, nasal secretions and brain. The direct FRA stain of brain tissue at autopsy was also positive. Serum rabies antibody titers rose from <1:4 to 1:4,096 when measured by the indirect fluorescent antibody technique, and from 1:16 to 1:16,384 by the fluorescent foci inhibition technique. Rabies antibody was also detected in the sputum, cerebrospinal fluid, and a homogenate of brain tissue obtained at autopsy.

Discussion

Clinical Features

Rabies is an acute viral meningoencephalitis usually resulting from the inoculation of the rabies virus, present in the saliva of the biting animal, into the muscle or subcutaneous tissues of the victim. Infection may also result from mucous membrane inoculation.[4] The virus passes via spinal nerves and dorsal root ganglia to the spinal cord, then to the brain.[5,6] Centrifugal axoplasmal neural spread follows and the virus may be distributed to the retina, cornea, parafollicular nerve endings, salivary glands, brown adipose tissue, lung, liver, kidney, skeletal muscle, adrenal medulla, myocardium and pancreas.[5,7] The incubation period is usually 20 to 60 days but has been reported to be as long as 19 years.[8-10] The validity of these longer incubation periods is doubtful. This patient's prolonged incubation period of approximately one year is unusual. The longest reported incubation period for the 253 cases of human rabies in the United States in the past 30 years was 270 days,[11-13] if one excludes the patient with a questionable incubation period of 23 months, who may have been reexposed to a rabid fox six months before his death.[11]

This patient's initial symptoms, headache, anorexia and fever, were nonspecific. Nonspecific symptoms are regularly part of the rabies prodrome (Figure 1).[12,13] The paresthesias of the plantar surface of the left foot implied a bite in this area; at least 50 percent of rabies patients present with paresthesias at the site of inoculation.[14] The history of difficulty in swallowing food and water, of confusion and of auditory hallucination, and her observed behavior, suggested the acute neurologic phase of clinical rabies. However, the repeated denial of animal bite, the long interval since residing in a rabies endemic area, and the ability to swallow water and pills when coaxed by the nursing staff, led the admitting physicians to believe the hydrophobia was functional.

Following the onset of the acute neurologic phase, the patient became more lethargic and an ascending paralysis developed similar to the Guillain-Barré syndrome, previously reported in rabies patients.[1,15] Frequent periods of apnea then developed, requiring assisted ventilation, and in 36 hours a total flaccid paralysis ensued. Such rapid deterioration is characteristic.

This patient had the pulmonary, neurologic and cardiac complications of human rabies. The initial arterial blood gas studies revealed a low oxygen pressure, low carbon dioxide pressure and a high pH in the presence of hyperventilation. Subsequently, bronchopneumonia and pneumothorax developed. The low arterial oxygen pressure and respiratory alkalosis, frequently observed in rabies victims, are thought to be secondary to ventilation-perfusion abnormalities.[16] Secondary bronchopneumonia and pneumothorax are recognized complications of assisted ventilation and occur in patients with prolonged survival with rabies. Neurologic complications include hypothermia, diabetes insipidus, and generalized seizures. The impairment of thermo-regulation and diabetes insipidus were postulated to be secondary to alteration of the homeostatic mechanisms of the hypothalamic-pituitary axis.

Cardiovascular complications were most difficult to manage. Bradycardia and hypotension, at first responsive to atropine and isoproterenol, became resistant to all concentrations of these agents, and cardiac arrythmias, including A-V dissociation and junctional rhythms, proved to be the cause of death. Results of postmortem examination of the heart were consistent with myocarditis. Myocarditis occurs in rabies victims and was reported

to be present in 22 percent of patients in one series.[17-19] The virus has been shown to be present in the myocardium of 58 percent of patients in one series of human rabies cases.[7] Cardiovascular complications are probably due to myocarditis, and hypothalamic alterations in vasomotor reflexes.

Laboratory Diagnosis

The diagnosis of rabies is dependent upon showing the presence of the rabies antigen, by viral isolation in mice or cell cultures, electron-microscopy or immunofluorescent rabies antibody staining. The development of significant antibody titers is also diagnostic. In patients who have never received rabies vaccine or passive antibody (equine or human), any antibody titer is confirmatory. Cerebrospinal fluid rabies antibody titers are also diagnostic of rabies,[1,2] and have been used to differentiate human rabies from postvaccination encephalomyelitis.

Table 1 lists the laboratory tests done in this case to confirm the presence of rabies virus. The corneal touch preparation is highly specific in the hands of qualified personnel;[20,21] however, in a recent summary of human rabies, this method was positive in only three of seven patients (43 percent).[22] In this case, corneal cell preparations obtained on two successive days early in the illness were negative.

A more recently described technique is the identification of the rabies antigen in parafollicular neurons of skin biopsy material by FRA staining. This method is predicated upon the rapid centrifugal neural spread of rabies virus from the brain to nerve endings associated with hairs about the head.[5] Smith showed that this technique gave positive results in 100 percent of experimentally infected mice as early as four days before onset of clinical symptoms.[23] Biopsies taken from hairy cheek skin of three rabies patients, with diagnosis confirmed by viral isolation, were reported to be positive using this technique.[3] In this patient the diagnosis of rabies also was confirmed by this technique on the tenth day of illness (test was carried out by Dr. Donald Blendon of the University of Missouri).

Rationale for the Care of Case Contacts

The transmission of rabies virus to man is usually limited to animal bite exposures. However, three cases in the United States have been

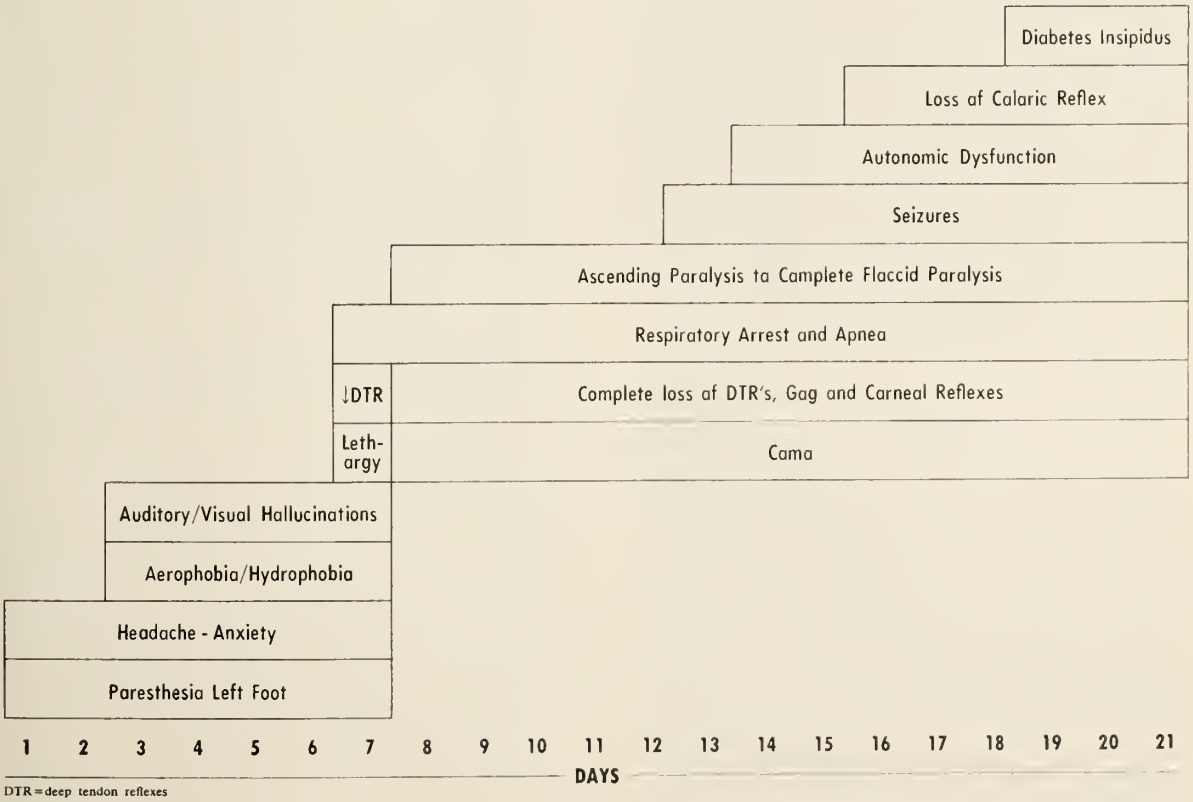

Figure 1.—Clinical signs and symptoms.

attributed to the airborne route of transmission. Two of these cases occurred in persons who investigated caves in Texas inhabited by insectivorous bats known to harbor rabies virus.[24-26] The other aerosol exposure occurred in a laboratory worker homogenizing rabid sheep brain for vaccine production.[27] There is only one report (of uncertain validity) of person-to-person transmission of rabies.[28]

Because rabies may be inoculated via mucous membranes, and virus is present in the saliva of humans with rabies, transmission from patient to family members and hospital personnel must be considered a possibility, and appropriate isolation precautions should be employed to protect personnel. Inappropriate fear of the patient should be prevented by staff counseling and education.

All personnel caring for this patient wore masks, gowns and gloves. This was especially important when providing tracheal care and oral hygiene. We interviewed all hospital personnel and patients who had contact with the patient before the diagnosis of rabies to determine the nature of their exposure. All were informed of the absence of human-to-human spread in medical care settings. Only two persons were found in whom prophylactic immunization was warranted. One was an adolescent patient whom this patient had kissed vigorously with exchange of saliva, and then later scratched. The other was a resident physician who had contaminated a deep fresh laceration of her finger with the patient's saliva. Both received rabies immune globulin (human), 20 IU per kg of body weight, and 23 doses of duck embryo rabies vaccine, and in both there were adequate rabies antibody titers one month after immunization began.

Summary

In a 16-year-old girl, with no initial history of animal exposure, human rabies encephalitis developed. She died after 21 days despite intensive hospital care. She had received no postexposure rabies prophylaxis. The probable incubation period of approximately one year in this case is distinctly unusual and led to a delay in the diagnosis. Complications included the Guillain-Barré syndrome, hypothermia, diabetes insipidus, cardiac arrythmias and hypotension, ventilation-perfusion abnormalities, and secondary bronchopneumonia. The initial diagnosis was made by FRA staining of a skin biopsy specimen from the posterior nuchal region after corneal touch preparations were negative. The patient was isolated, with hospital personnel using masks, gowns and gloves. Two case contacts, a physician and another patient, had significant exposure to the patient and received rabies prophylaxis with hyperimmune human serum and duck embryo vaccine. The hospital management and pathophysiology of this illness are discussed in detail.

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Acute Suppurative Thyroiditis

Diagnostic, Metabolic and Therapeutic Observations

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ALTHOUGH acute suppurative thyroiditis has been seen infrequently in the antimicrobial era, this disorder presents diagnostic and therapeutic problems which must be rapidly solved in order to permit optimal treatment. The clinical, endocrine and scintiphotographic features of acute suppurative thyroiditis, as well as its treatment and natural history, are the subjects of this report.

Report of a Case

A 38-year-old woman was admitted to the University of California, Davis-Sacramento Medical Center following a ten-day illness characterized by fever, sore throat, dysphagia and erythema of the anterior neck. After the onset of cervical tenderness, the patient noted the development of nervousness, anorexia, weight loss, hoarseness, chills, palpitations and extreme lethargy. There was no known history of goiter or previous thyroid disease. The patient had been taking primidone, 250 mg three times a day, intermittently for a posttraumatic seizure disorder. There was also a history of gastrointestinal bleeding, ethanol abuse and surgical correction of severe thoracic scoliosis.

On examination the patient was in moderate distress, sitting upright with the neck flexed anteriorly. The pulse was 120 beats per minute and regular, blood pressure was 110/70 mm of mercury and temperature taken orally was 38°C (100.4°F). Ocular examination showed a stare and lid lag but exophthalmometry gave normal findings. The pharynx was erythematous without exudate. The skin overlying the thyroid was tense and red. The jugular veins were distended. The thyroid was exquisitely tender and diffusely enlarged, with an estimated weight of 80 grams. There were no palpable nodules or areas of fluctuance. No bruit was audible and cervical lymph nodes were not palpable. The chest was clear to percussion and auscultation. Cardiac examination showed a regular rhythm and a grade II/VI ejection murmur. There were no extracardiac sounds. The liver was slightly enlarged and tender. A spleen tip was palpable below the left costal margin. The extremities were thin and wasted but without edema. A fine resting tremor was present. The deep tendon reflexes were brisk and symmetrical.

Admission laboratory data included a leukocyte count of 25,400 per ml with 34 percent bands, 51 percent segmented polymorphonuclear leukocytes, 5 percent lymphocytes and 10 percent monocytes. The erythrocyte sedimentation rate (Westergren) was 128 mm per hour. The hematocrit reading was 34.5; hemoglobin, 11.8 grams per 100 ml; sodium, 131 mEq per liter; potassium, 2.7 mEq per liter; chloride, 90 mEq per liter, and bicarbonate, 24 mEq per liter. Analysis of urine showed 1+ proteinuria. An electrocardiogram showed a sinus tachycardia at a rate of 140 and low voltage. On an x-ray study of the chest a right lateral thoracic scoliosis was noted with a Harrington rod in place. Bilateral apical pleural thickening was noted. Roentgenograms of the neck showed no widening of the prevertebral soft tissues; no abnormal gas accumulations were seen.

Initial thyroid function tests gave the following values: thyroxine (T_4) 4.8 μg per 100 ml, triiodothyronine (T_3) resin uptake of 29.3 percent and a free thyroxine index (T_7) of 1.4 units. The thyrotropin (TSH) level was less than 3.3 μU per ml. The protein bound iodine (PBI) level was 6.4 mg per 100 ml, and a 24° radioactive iodine (RAI) uptake was 3 percent. Subsequent thyroid data as well as the range of laboratory normals are indicated in Table 1.

Initially the differential diagnosis included acute suppurative thyroiditis, subacute (nonbacterial) thyroiditis and thyrotoxic Graves disease. This

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clinical presentation was further complicated by the possibility of acute ethanol withdrawal. The patient was treated with acetaminophen (600 mg. given orally every four hours), propranolol (20 mg given orally four times a day), and diazepam (5 mg given orally three times a day); a regimen of primidone (250 mg given orally three times a day) was maintained. On the second hospital day the patient's temperature was 39.3°C (102.8°F) and subsequently acute respiratory failure developed, presumably due to upper airway obstruction. Treatment with orotracheal intubation and ventilatory assistance was begun. Intravenous administration of nafcillin (2 grams every four hours) and hydrocortisone (1 gram immediately, then 250 mg every six hours) was instituted. Blood cultures taken on the first hospital day yielded group A β hemolytic streptococcus and penicillin (1 million units every four hours) was substituted for nafcillin. Her course over the next few days was marked by general improvement and the gradual development of fluctuance over the right lobe of the thyroid. On surgical exploration on the sixth hospital day a multiloculated abscess within the thyroid capsule was noted. This was explored by blunt dissection and three Penrose drains were left in place. Pus from the abscess yielded group A β hemolytic streptococcus. The temperature became normal four days after the initiation of antimicrobic therapy which was continued for a total of 13 days. The inflammation resolved gradually and the patient was discharged three weeks after admission.

Thyroid studies done at the time of discharge showed a T_4 of 2.9 μg per 100 ml, a T_3 resin uptake of 29.2 percent and a T_7 of 0.8 units. A TSH was 12 μU per ml and a repeat 24° RAI uptake was 18 percent while a scan showed patchy thyroid uptake with a defect in the right lower lobe of the thyroid (Figure 1). Additional laboratory data showed the antistreptolysin titer to be greater than 250 Todd units. Antibody titers to mumps soluble and viral antigens were positive at a dilution of 1:8 in acute and convalescent sera.

Discussion

Acute suppurative thyroiditis was first described by Bauchet in 1857.[1] Several early reviews[2-4] indicate that the disease was more common in the preantimicrobial era. However, it is likely that some of these cases were subacute thyroiditis, a more common disorder. Streptococcus pyogenes, Staphylococcus aureus and the pneumonococci are the three organisms most commonly cultured from suppurative thyroiditis.[5,6] Although less common, a wide variety of other bacteria have been isolated including Salmonella typhosa,[3,7] S. paratyphi A and B,[3] S. enteritidis,[8] Hemophilus influenzae,[9] Escherichia coli,[6] Klebsiella species,[10] Streptococcus viridans,[11,12] Actinomyces naeslundi[13] and Mycobacterium intracellulare.[14] Anaerobic bacteria isolated from thyroid abscesses included Bacteroides fragilis[15] and B. melaninogenicus;[16] gas formation has been reported with the isolation of Clostridium septicum[17] and in one case with the recovery of foul smelling pus which yielded no organisms on culture.[18] The thyroid has also been involved in such chronic infections as tuberculosis, syphilis and echinococcosis.[6,19]

The infecting agent may reach the thyroid via the blood, lymphatics, spread from contiguous structures, direct penetration due to trauma or from a persistent thyroglossal duct. The thyroid is quite resistant to infection when bacteria are injected directly into the thyroid arteries,[20] although underlying thyroid disease may enhance susceptibility. In one review[5] half of the patients

TABLE 1.—*Thyroid Function Tests*

Interval from Admission	*T_4* (3.0-11.0 μgm Percent)	*T_3 RU* (22-33 Percent)	*T_7* (1.0-3.0 units)	*TSH* (3.3-8.0 μU/ml.)	*Total T_3 RIA* (60-200 ng/dl)	*24° RAI Uptake* (12-35 Percent)	*PBI* (4.0-8.0 mcg/dl)
1 day	4.8	29.3	1.4	<3.3	70	3	6.4
5 days	2.1	46.5	1.0			<1	
11 days	4.1	33.7	1.4	7.5			4.2
2 weeks	3.1	33.9	1.1	9.2	77		
3 weeks	2.9	29.2	0.8	12.0		18	
6 weeks	3.1	26.8	0.8	10.0			
6 months	2.3	26.4	0.6	6.9	105	12	
9 months	2.6	31.6	0.8	6.3			

T_4 = thyroxine
T_3RU = triiodothyronine resin uptake
T_7 = free thyroxine index
TSH = thyrotropin
RAI = radioactive iodine
PBI = protein bound iodine

with suppurative thyroiditis also had adenomatous goiters and in these patients the infection was localized rather than diffuse.

Suppurative thyroiditis occurs most often in females[2,3] and the highest incidence is found in the 20 to 40 age group.[3,5] The disease is characterized by the abrupt onset of fever, chills and local signs of inflammation in the neck. Pain is usually severe, may be referred to the ear, mandible, or occiput, and is often aggravated by extension of the neck. Dysphagia and hoarseness are common. Most often the patient appears to be acutely ill with fever, tachycardia and pronounced leukocytosis. It is often difficult to differentiate this disorder from the more common subacute thyroiditis, which is generally a milder disease with less toxic manifestations, because either disease can present with widely varying severity. The PBI, T_4 and erythrocyte sedimentation rate are usually elevated in early subacute thyroiditis; the gland is diffusely involved and the radioiodine uptakes are classically low.[21] However, all of these features may be present in acute suppurative thyroiditis. Differentiation is important because suppurative thyroiditis is usually a progressive disease which may be complicated by septicemia, airway obstruction, rupture of the abscess or septic thrombophlebitis. Subacute thyroiditis on the other hand is usually a self-limited disorder leading to recovery without complications within two to four months;[22] usually, symptomatic treatment with analgesics or rarely corticosteroids is sufficient. Certainly, in a suspected case of unusual severity, blood cultures should be obtained. A lateral roentgenogram of the neck may help localize the area of inflammation to the thyroid and may show the presence of gas. Needle biopsy of the thyroid has been useful in making the diagnosis of suppurative thyroiditis and yields material for culture.[23] Because Gram-positive pyogenic cocci are most often responsible for suppurative thyroiditis, and penicillinase-producing staphylococci are prevalent in nonhospital environments, initial treatment with intravenous administration of nafcillin is recommended while results of bacterial cultures are pending. Corticosteroids may be useful in the presence of septicemia and shock.

Thyroid function (Table 1) during the course of acute suppurative thyroiditis is not well described in the literature. It is generally stated that the patient is euthyroid and radioiodine uptakes are normal.[24] These observations are often utilized to differentiate this disorder from subacute thyroiditis where thyroid dysfunction is usually found as noted above. However, an increase in the level of serum T_4 may occur in acute suppurative thyroiditis from the release of preformed products into the circulation.[25] The RAI uptake may be reduced only over the abscess[25] or, as in this case, the total uptake may be low. In our patient there clearly were low radioiodine uptakes early in the course of illness and transient hypothyroidism as indicated by the elevation in plasma TSH (Table 1). This low radioiodine uptake suggests that the process was diffusely disrupting follicular function. However, a scan carried out three weeks after admission showed only the residual defect laterally compressing the right lobe where the abscess developed (Figure 1). Several other cases of acute suppurative thyroiditis, also had corresponding low RAI uptakes during the acute illness.[12,14,16,26,27] We suggest that the radioiodine uptake can be notably suppressed in acute suppurative thyroiditis and that the value is of little use in differentiating this disorder from subacute thyroiditis. On the fifth hospital day a reduced

Figure 1.—Thyroid scan done three weeks after admission showing defect in the lateral right lobe.

T_4 but elevated T_3 resin uptake was observed. This may in fact reflect stress induced depression of thyroid binding prealbumin.

In conclusion, it may not be possible with noninvasive procedures to positively differentiate acute suppurative thyroiditis from other thyroid disorders. Because of the desirability of prompt antimicrobial therapy for acute suppurative thyroiditis, blood cultures and early biopsy should be considered.

Summary

The case of a patient with group A β hemolytic streptococcal infection of the thyroid is reported. The literature pertaining to acute suppurative thyroiditis is reviewed and problems in differentiating this diagnosis from subacute (nonbacterial) thyroiditis are discussed. It is concluded that positive differentiation of acute suppurative thyroiditis from other thyroid disorders may not be possible with noninvasive techniques. The desirability of prompt antimicrobial therapy for acute suppurative thyroiditis requires early consideration of blood cultures and biopsy.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Mesothelioma in Shipyard Workers

To the Editor: Mesothelioma of the pleura and peritoneum is still considered a rather rare pathologic entity although there is evidence that the incidence is increasing.[1] The association of mesothelioma with exposure to asbestos has been confirmed and found to be very strong in many parts of the world.[2] Workers in shipyard occupations, where asbestos has been used extensively for insulation of the steam plant of ships, have been shown to have an increased risk of mesothelioma by several investigators.[2]

The purpose of this communication is to document the expected excess of mesothelioma among shipyard workers of the Puget Sound area in Washington state and to show the simplicity of doing so using only readily available vital statistics documents.

All death certificates with mesothelioma listed as a cause of death were identified for the years 1968 through 1976 for four counties in the Puget Sound region of Washington. From each death certificate the age and usual occupation of the person were obtained. Two matched controls were chosen for each case by proceeding forward in the death files and selecting the first two certificates that matched the case certificate for sex, ten-year age group and county of residence at death, as well as showing a diagnosis other than mesothelioma.

Tests of significance were carried out according to the methods of Miettinen as recommended for individual matching with two or more controls.[3]

Totals of 40 cases in men and 12 cases in women were found for this study period. The mean age of these men was 66.2 ± 10.8 years and of the women, 60.5 ± 14.5 years. The number of cases in men and the approximate mesothelioma death rates per million men age 30 and over for each county are the following: King, 24 and 10.2; Kitsap, 9 and 42.1; Pierce, 6 and 7.8; Snohomish, 1 and 1.9.

The analysis of occupations shows no significant results for women or for male residents of Pierce or Snohomish counties. However, analysis of occupations of male residents of King and Kitsap counties combined indicates that in 30.3 percent of cases the men were employees of the Puget Sound Naval Shipyard (PSNS) in Bremerton, Washington (Kitsap County), as compared with only 7.6 percent of controls. With a two-tailed test and continuity correction applied this is a significant difference ($p<0.01$).

A similar analysis of Kitsap county cases alone also shows a significant ($p<0.02$) excess of persons with mesothelioma to be employees of PSNS (88.9 percent of cases versus only 22.2 percent of controls). Analysis of King County cases alone does show an excess of PSNS employees (8.3 percent of cases versus 2.1 percent of controls), but the difference is not significant.

The results of this study are in agreement with previous investigations which indicated that shipyard workers are at increased risk of mesothelioma developing. This is, however, the first published report of the association between shipyard workers of the Pacific Northwest and mesothelioma and indicates a small epidemic of mesothelioma cases in Kitsap County, Washington.

A great variety of occupations were found among the mesothelioma cases in persons employed by PSNS, including ship fitter, foreman, rigger, foundry worker, boiler maker, engineer, maintenance supervisor, pipe fitter and sheet metal worker. This variety of occupations probably indicates that significant indirect exposure to asbestos was common among shipyard workers during World War II and immediately thereafter. However, the actual type of work done 20 or 30 years before the death of the men in these cases is uncertain because death certificates only show the kind of work done during most of the deceased person's working life.

Occupational exposure to asbestos has been coming under increasing control over the past three decades and more stringent standards have

been forthcoming as our knowledge of the health effects of exposure increases.[4] Chronic diseases, and in particular cancer, are a major cause of morbidity and mortality in industrial nations. The control of occupational carcinogens can contribute significantly to a reduction of the future cancer burden. Although this study was not carried out to test a new hypothesis of occupational carcinogenesis, but rather to document a proven relationship in a population not previously examined, the method used can be a quick and simple approach when a occupational cause of a lethal disease is suspected.

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Information Systems for Small Medical Communities

To the Editor: The letter "Concerning Libraries in Smaller Hospitals," which appeared in the December 1977 issue, was of great interest to us. While several hospitals may employ a single librarian to rotate among them, unifying a library system within these hospitals is only one solution to the problem. For those facilities that have the financial fortune to afford a librarian the problem is resolved. However, most communities neither have the financial capacity nor the personnel with credentials to undertake such a project.

In the contemporary era where the body of medical knowledge grows in great proportion each day there is a library need to be met in many medical communities without the asset of a librarian. The reference made to conference rooms or physicians' lounges with bookshelves crammed with outdated medical texts and old journals is too frequently a sad reality. Someone must maintain the library—either a permanent or rotating librarian, or, as we shall suggest below, designated personnel.

Using our family practice center of 13 generalists, 7 specialists, 2 family nurse practitioners and 1 physician's assistant as an example, we would like to give our solution of the library problem. It should be noted that our facility is a preceptor site for the medical students and family nurse practitioners for the University of California campuses of Irvine, Davis and San Francisco, as well as for the physician's assistant program at Stanford University. As a teaching-training facility we are obliged to maintain extensive and readily accessible educational resources for ourselves and our preceptees.

We approached the library situation from three angles. Our first source of medical literature is our library (with its standard texts of anatomy, physiology, specific diseases and treatments), which is quite rudimentary. However, we extended our library beyond the medical school texts to the practical integration of diseases by purchasing a basic set of the Harper & Row's encyclopedias which cover all fields of medicine. These encyclopedias are clinically oriented and periodically updated with annual supplements, in addition to monthly international medical and surgical digests, complemented by a consulting bureau for literature needs, provided free of charge to all active subscribers. With this service outdated medical texts can be eliminated.

Second, we instituted a Master Medical Index System, which is an expansion of the Master Medical Index System designed by References and Index Services, Inc. for maintaining abstracts. This source covers every phase of medicine, subdividing into the different anatomical systems which are ultimately subdivided into specific diseases and therapeutic entities. Frequently overlooked aspects of medicine—that is, historical and social factors, new concepts and innovations, and whatever modifications one might wish to emphasize—are included.

This method is not costly to maintain, nor does it require a librarian. The index system is conveniently alphabetized and requires minimal space, as compared with a library of books and bound journals covering the same information. We are using eight 4-foot file cabinets. Each month members of the group contribute from their particular journals pertinent articles, which insures new and current material being available. As an example, a contributor may submit an article related to feeding problems of premature newborn infants. This article, representing the most recent concept in this field, would be filed in the Pediatric Section under: A. Newborn, 2. Premature newborn, b. Feeding—along with many other articles relative to the same topic. This system represents over 20 years of concepts, therapies and trends, and

makes available to physicians or students an array of articles upon which they can base research and bibliography.

Our third source of medical literature is the computerized photography libraries. The American Medical Association library has always granted requests for reprints, and now provides us with computerized searches of the medical literature through the Medline System of the National Library of Medicine. This resource is available to all AMA members and can be obtained either by letter or a telephone call. Telephone requests procure the material within five days. Our library also includes an audiovisual unit with programmed cassettes for staff and patient viewing, together with cassette programs from the Audio-Digest Foundation.

The total cost for this continuing, self-sustaining system was less than $5,000 to implement and its yearly maintenance averages $500.

Our system provides a broad perspective of multi-sourced information, is not expensive and offers an answer for small urban and rural medical communities to the problem of inaccessibility to a major library.

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Informed Opinion or Assault?

To the Editor: A patient has the right to know what his doctors are planning to do to him. And his doctors have the responsibility to inform him sufficiently of the risk/benefit ratio so his consent has some meaning. Scaring hell out of the patient by dwelling on risks, however, is as evil a practice as the "I am God and don't need to tell you what I'm doing" attitude it is intended to replace.

For example, an over-zealous anesthesiologist, who describes in almost sadistic detail the risks being taken is not serving the patient through informing him; rather, he is assaulting the patient as he himself strives to escape responsibility in case an untoward result occurs. There is a world of difference between a responsible presentation of risks and an excessive detailing of them.

There is no doubt about it, we are in a risky business. It *can* hurt somebody. Yet, we should not take refuge in laying off our responsibility on the patient. If we choose to respond to legal maneuvers by acting like technicians instead of compassionate professionals, then the path to being treated like technicians won't be long or far away.

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More on Health Practitioners

To the Editor: I must commend Drs. Kane and Wilson for their timely article, "The New Health Practitioner—The Past as Prologue" (West J Med 127:254-261, Sep 1977). Indeed, primary care activities are now being carried out by nonphysician personnel, such as nurse practitioners and physician's assistants, allowing the public more adequate coverage for health care delivery. However, the authors stated that "local pharmacists may be called upon to prescribe . . . as well as to dispense." This is misleading. Though many pharmacists are knowledgeable enough to prescribe, by law, they are not allowed to.[1] True, pharmacists may advise physicians about the most efficacious ways of determining dosages of medications utilizing pharmacokinetic calculations and their up-to-date knowledge of the medical literature. Pharmacists have also written out prescriptions for drugs after evaluating patients, but these had to be countersigned by a physician.[2]

Interestingly, it has been predicted[3] that by the year 2000 the physicians' patient load will be so large that prescribing activities will have to be in the pharmacists' hands. Surely, the soda jerk druggist may still exist, but I doubt if 20 years from now *he* will still come under the classification of "pharmacist." I feel that if a pharmacist with the present doctorate degree is allowed to practice, right out of college, directly with patients, all those years of taking classes alongside medical students and all his added expertise in pharmacology will not fall by the wayside and be forgotten.

Meanwhile, today's pharmacists have shown physical assessment abilities in Indian Health Service Centers,[4-6] and have been of great value on cardiopulmonary resuscitation teams;[7] in drug information centers;[8] and in hypertension,[9,10] oncology[11,12] and diabetes[13,14] clinics. Just how widespread these activities will become by the year 2000, no one can say. But, I do believe that even

though their future contribution to patient care will be considerable, pharmacists and members of each of the other health disciplines should not try to completely "replace" the physician.

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The Contingency Fee

To the Editor: The recent recommendation by the California Citizens Committee on Tort Reform (CCCTR) to the California Medical Association's House of Delegates in Los Angeles that the contingency fee be retained was the only unpleasant surprise in an otherwise outstanding report. Even more disturbing was the fact that the House of Delegates concurred and actually defeated a proposal to condemn contingency fees on principle.

This action has to be a source of concern to anyone familiar with tort law. Justification of the contingency fee is based on the triad of "it is the poor man's key to the courthouse," "it discourages frivolous law suits" and "there is no alternative." Like most shibboleths that are never questioned, it is easily shown that these cliches are false. It is obvious that the contingency fee is not every poor man's key to the courthouse but only the key to that small percentage of poor men who have injuries sufficiently severe—that is, potential awards sufficiently large—to arouse some attorney's avarice. Furthermore lawyers are not obligated to use the contingency system; they may contract for a prepaid fee if it suits their convenience. The rich man may still obtain legal aid by the contract system where his lawyer does not feel the reward/risk ratio warrants use of the contingency fee. The poor man cannot. This is discrimination against poor or middle class litigants who are not severely disabled. It produces unequal access to justice based on wealth and circumstance.

The contingency fee is a capricious mechanism for discouraging nuisance suits because it is designed to encourage lawyers to accept cases on the possibility of a substantial award rather than on the basis of legal merit. It sacrifices the plaintiff's access to the courtroom and the defendant's protection against unwarranted litigation to a lawyer's decision to gamble his skill and case preparation costs against the chance of a sizable judgment. It is a rare lawyer who will not wager $15,000 preparation costs against 30 percent to 40 percent interest in a $1,000,000 settlement, even though there may be only nuisance value in the tort. Ambitious lawyers will often prosecute what previously has been an unmeritorious action in the hope of obtaining a valuable precedent. Indigent lawyers may take frivolous suits because they have nothing to lose. Ignorant lawyers prosecute cases with no merit because they do not know what merit is.

Personal injury suits are not always frivolous because the potential awards are small. A valid injustice, even though it be small, rankles as much as a large one. The boundary between "nuisance" and "significant" varies with the economic status of the observer. It is here that the two useful social functions claimed for the contingency fee come into conflict. It cannot act to screen nuisance suits without blocking the poor man's access to the courtroom; it cannot allow equal access to the courtroom without permitting nuisance suits.

One valid point made in Los Angeles was that from a tactical standpoint an attempt to eliminate the contingency fee would arouse such ferocious opposition as to jeopardize passage of the CCCTR package as a whole. Therefore it may be wise not to push for abolition at this time. However, it is important to distinguish between tactics and strategy and between compromise and integrity. To publicly express approval of the contingency fee is poor strategy because it will handicap any future efforts to eliminate it. Even more important, up to this point, physicians have successfully maintained an image of moral superiority in conflict with other groups over tort reform. To now

affirm that the contingency fee is a good system when doctors know it is a bad one is a surrender of integrity. This is particularly unwise because sooner or later the inequities of the system will become common knowledge. When this happens organized medicine will lose credibility and will sink in the public's estimation to the same ethical level as its opponents.

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FDA—The 11th Myth

To THE EDITOR: This communication is occasioned by the publication of Food and Drug Administration (FDA) Commissioner Donald Kennedy's essay entitled "Ten Medical Myths About FDA," as well as by the editorial comment on the article, both in the December issue. After reading Commissioner Kennedy's statements to physicians, several comments seem most germane. I claim no expertise in most of the FDA's controversial activities (cyclamate, Laetrile) but do have some first hand knowledge of their behavior involving Controlled Substances (psychotropic drugs).

The Food, Drug and Cosmetic Act initially gave the FDA responsibility for insuring safety and efficacy of products that cross lines of interstate commerce. However, an attempt is now being made to extend these boundaries to include control by consideration of (real or fantasied) drug abuse risk/benefit in the country. Consequently, as recently as December 2, 1977, public hearings were held by the FDA in Washington with the intent of strictly limiting the use of amphetamines to narcolepsy and hyperkinesis. This represents an attempt by the FDA to abolish their use in obesity, depression and other conditions. These hearings were based on peculiarly "massaged" data published in the *Federal Register,* some challenged by subcontractors of the FDA and Defense Enforcement Administration and some —the Drug Abuse Warning Network (DAWN) data—openly acknowledged to be, at least in part, false. In addition, senior officials of the FDA are reported to have said that physicians who do not conform will be "open to medical malpractice."[1] One physician, Dr. Arnold Mandell, has already been prosecuted in California for prescribing amphetamines to *already drug abusing* football players in a psychotherapeutic strategy designed to get them drug free. Strong emphasis at the Board of Medical Quality Assurance administrative hearings was placed on the fact that Dr. Mandell did not adhere to the *Physicians' Desk Reference (PDR)* precise guidelines. Although FDA Commissioner Charles C. Edwards in 1972 in the *Federal Register* repudiated adherence to package inserts (and the *PDR*) as the ultimate guide to sound medical practice, and reemphasized clinical judgment as its ultimate source, the FDA seems to be fostering a movement away from that policy. The physician in charge of the FDA amphetamine hearings, after hearing testimony about the Mandell situation, stated openly that the FDA *made* regulations, but was not responsible for what happened to them thereafter (that is, we just built an atomic bomb, but it is not our responsibility who drops it).

An additional area of bureaucratic bumbling is the overlapping of the two FDA Controlled Substances committees and their "Catch 22" approach to marijuana research. This has led to the White House creation recently of a special National Institutes of Health committee to handle such problems, created in large part by the FDA. Specifically, I refer to their refusal until now to allow women of childbearing potential to enter marijuana chemotherapy research projects in cancer patients, despite the known teratogenic effects of the chemotherapeutic drugs. And, despite years of efforts by the scientific community, FDA has refused to agree to change marijuana from its Schedule I Controlled Substance classification (along with heroin and LSD) which, besides its absurdity, continues to bode ill for the research and treatment communities. FDA officials have also repeatedly stated that even at such time as Phase III studies have proven marijuana's medical usefulness, they will delay removing marijuana from Schedule I until a new drug application is filed (maybe another seven years). This, in almost all cases, depends upon a pharmaceutical company doing the necessary work to apply, which traditionally has rested on free enterprise and (understandably) a profit motive. But what about the patient, in the meantime?

I hope that physicians in all states are not deceived by fine words and offers of increasing communication without any commensurate action. In summary, the "11th myth" well may be that Commissioner Kennedy's ten medical myths really are only myths.

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Abraham Lincoln and Cardiac Decompensation

A Preliminary Report

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IN A PREVIOUS ARTICLE evidence was given showing that aortic insufficiency was present in Abraham Lincoln two years before his violent death.[1] It was also considered in that article that the President's declining health in office was best explained by a decrease in cardiac reserve rather than by psychic stress as generally assumed historically. While no specific supporting information relating to myocardial decompensation was then offered, evidence is now available indicating that at the time of his assassination, Lincoln was in an early stage of congestive heart failure.

Background and Critical Evidence

Published in 1964, a genetic study of the Lincoln family established that the unusual morphologic characteristics of President Lincoln—both skeletal and visual—were manifestations of the Marfan syndrome.[2] Only later was evidence for a cardiac lesion found in Lincoln, and it is significant that this involvement, aortic insufficiency, is a common complication of arachnodactyly, that is, the Marfan entity. The actual evidence was based upon a photograph and various related remarks and observations of the President, all of which were consistent with a highly diagnostic sign: hyperdynamic, abnormally bounding peripheral arterial pulsations.[1] Since in any case of longstanding aortic insufficiency certain cardiovascular sequelae are to be anticipated clinically, it is of consequence that precisely such developments can now be shown in the case of Lincoln. The critical material is found in the President's own words, virtually in the form of a past history and presenting complaint.

Some seven weeks before the assassination, Joshua Speed, Lincoln's most intimate friend, was witness to a highly emotional episode in which two persistent ladies implored the President to pardon a group of draft resisters. As soon as the women departed Speed spoke up: " 'Lincoln . . . it is a wonder such scenes as this don't kill you.' And the President after a thoughtful moment replied: 'Yes, you are to a certain degree right, I ought not to undergo what I so often do. I am very unwell now; my feet and hands of late seem to be always cold, and I ought perhaps to be in bed; but things of the sort you have just seen don't hurt me, for, to tell you the truth, that scene is the only thing today that has made me forget my condition or given me any pleasure.' "[3]

Exposition

Taken in the context of the Marfan syndrome and aortic insufficiency, Lincoln's remarks assume considerable pathologic significance. While a person with aortic regurgitation may live many years essentially asymptomatic and without congestive failure developing, ultimately the burden on the myocardium is such that various compensatory mechanisms become manifest. One related mecha-

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nism is sympatho-adrenal reflex vasoconstriction of peripheral arteries with the shunting of blood away from the skin and skeletal muscles of the extremities so as to perfuse more adequately the brain and other vital organs.

As mentioned in many cardiology texts, a clinical expression of vasoconstriction is cold hands and feet, just as Lincoln so clearly observed in himself. It is at this stage in the pathogenesis of aortic insufficiency that the myocardium is in a decompensating state. Other mechanisms also become operative at this time in an attempt to maintain the cardiac output. Together these may well —under less than physically stressful conditions— be temporarily effective, with episodic bouts of congestive failure and recovery occurring during greater and lesser periods of rest or activity. However, from the point at which compensatory mechanisms come into play, the natural course of the disturbance though intermittent, is relentlessly progressive. Hurst and Ladue in fact specifically state of aortic insufficiency that during severe decompensation the patient's cool pale extremities suggest vasoconstriction, and they add, "This syndrome is always most ominous."[4]

Returning to Lincoln's comments; his few words, no less than in some of his more celebrated speeches, are simply put yet fraught with meaning. Fully analyzed, the President's brief reply to Speed covers all the elements essential to a comprehensive understanding of Mr. Lincoln's failing health which previous to these studies had been attributed, for lack of other evidence, to the emotional strain of the presidency (see Figure 1). Most important, in using the phrase "my condition," Lincoln acknowledged his awareness of some underlying factor, not necessarily well-defined, that he correlated with the "late" onset of cold extremities; with being "very unwell" and with a need for bed rest. That condition it now appears was aortic insufficiency with ventricular overload and myocardial weakness.

1860 and 1865

The 1860 profile by Hesler, taken shortly after Lincoln's first nomination, is shown in contrast to a photograph by Gardner, one of several taken a few days before the assassination. The later face, wrote John Hay, had "a look as of one on whom sorrow and care had done their worst without victory."

Figure 1.—Side by side photographs (with original caption) as presented by Randall and Current in 1957 for purposes of physical comparison.[5] Hay's remarks reflect the "burden of office" theory of the President's failing health while the present evidence indicates myocardial decompensation secondary to aortic insufficiency and the Marfan syndrome.

In his last months of life, another striking change came over the President—easy fatigability. Activities which a short time before were a source of pleasure now exhausted him. As he himself most graphically described it after what had once been a daily routine: "When I get through with such a day's work there is only one word that can express my condition, and that is *flabbiness*."[3] In this regard Brest and Moyer, in discussing relatively severe aortic insufficiency, state that "A common initial complaint is unusual fatigue at the end of an average day's activity."[6] Extending this in the differential sense as it concerns mental strain, another authority offers that "sick fatigue" is "the earliest symptom" of chronic heart failure and is "sometimes mistaken for an emotional complaint."[7] Patients with the emotional form of fatigue, he emphasizes, complain of tiredness upon arising while those with heart failure develop such symptoms as the day progresses, even as did Lincoln.

Most important, fatigue was a condition unusual for this nonobese 56-year-old man who neither drank nor smoked and whose personality was suited, as no President before or since, to cope with the vicissitudes of high public office. All the several pathophysiologic findings given here, coming at a point when for the first time in years he was elated and mentally at ease as a result of his reelection and the imminent termination of the war, mitigate against a psychological cause for the President's loss of well-being. As Bertrand Russell observed: "To conduct a great war through years of difficulty and ill success, resolutely, to a victorious conclusion, and to remain throughout conciliatory and calm and large minded, is a feat which was accomplished by Lincoln, but, so far as I know, by no other historical character."[8] In Abraham Lincoln, emotional stress as a risk factor would appear to be minimal.

At this point it becomes appropriate for the clinician to ask: What if any additional factors may have accelerated the President's decline? Albeit highly circumstantial and still under investigation, certain evidence is available suggesting that subacute bacterial endocarditis may well have been the precipitating influence.

Shortly after his second inauguration, Lincoln's health became rapidly worse and he stayed in bed for several days.[9] And many eyes were upon the President and his every movement; newsmen, his cabinet, friends and, always, Mary Lincoln. All observed his deteriorating clinical status and, of many details,[10] a few only need to be considered at present.

On March 13, 1865, the *New York Herald* contained the following statement: "Mr. Lincoln is reported quite sick today and has denied himself to all visitors."[10]

On the 14th the Cabinet met in his bedroom and Bishop notes that "Mr. Lincoln tried to arise from his bed and fell back. He could not summon the strength to get on his feet. . . ."[11] This episode, consistent with a syncopal attack, prompted one physician many years ago to suggest this date as coinciding with the story of a faint experienced by Lincoln during these weeks.[8]

On March 15th the President was in his office conducting only the most urgent business. The next day, he was "still feeble" but took a short ride with his son Tad.[10] The remaining four weeks were filled with intermittent complaints, increasing fatigue and recurrent headaches.

Toward the end of his life, on March 23rd, in preparing a vacation for the President to "rest and convalesce"[9] Mrs. Lincoln said in a letter to Senator Sumner, "We cannot but fervently hope that change of air and rest, may have a beneficial effect on my good husband's health."[12] And only one day before their fateful visit to Ford's Theater, she wrote to General Grant of the President's "severe headache" and indisposition.[13]

Strange it is that during this illness of her husband, Mary Lincoln, among other extravagances, purchased a thousand dollars worth of mourning clothes.[14]

With complaints of being worn-out, of a fatigued feeling and again of a bad headache, on Good Friday, April 14, 1865, Abraham Lincoln had his last supper.[12]

Discussion

We have, then, a patient with the features of the Marfan syndrome plus bounding peripheral arterial pulsations, compensatory vasoconstriction, pathologic fatigue, headaches, a syncopal episode on arising and an intermittent progressive decline—all highly consistent with the pathogenetic course of an incompetent aortic valve.

Considering, therefore, the cumulative evidence, though incompletely given, it is highly likely that on the 13th and 14th of March, President Lincoln was in a state of early congestive heart failure which subsequently, if only temporarily, recom-

pensated with bed rest and decreased activity. In particular, the "always most ominous"[4] portents of cold hands and feet and the pathologic fatigue —both as an "initial"[6] complaint in aortic insufficiency as well as the "earliest symptom"[7] of chronic heart failure—cannot be diagnostically ignored. Neither can Lincoln's own awareness of some underlying "condition" as responsible for his symptoms.

Viewed organically rather than psychologically, many additional episodes in the Lincoln biographies assume a new perspective or take on meaning for the first time. Indeeed, a comprehensive medical reconstruction of the President's last two years in office, now in preparation, is even further consistent with a vast, currently little-known literature describing a multitude of gross and subtle findings in aortic insufficiency as seen before the advent of cardiac surgical procedures. Actually, the course of relentlessly advancing aortic insufficiency is today descriptively little taught and, in fact, is hardly vital for the generation of physicians involved with the technical apparatus of modern invasive and noninvasive cardiac diagnosis. Nevertheless, these reports on Lincoln may serve to emphasize, that the medical history remains as always a useful diagnostic technique associated with little morbidity and no mortality.

Among Lincoln scholars it is recognized that to understand truly the essential Lincoln one must study his own words. Idle words, however, were not a part of Lincoln's personality, neither in his speeches nor his pointed anecdotes, nor in his daily life. While "cold hands and feet," "flabbiness" and certain other expressions, including some suggesting angina, have been noted by many Lincoln biographers, they have been mentioned only in passing or at most in the overall context of emotional strain. Now, however, only one interpretation appears probable: a decompensating left ventricle which was the undiagnosed or concealed cause of the President's failing health.

Summary and Conclusion

In summary, the case of A.L., 56-year-old male statesman, may now be diagnostically classified in the manner recommended for all cardiac conditions.[15]

Etiologic diagnosis: Marfan syndrome
Anatomical diagnosis: aortic insufficiency
Physiologic diagnosis: myocardial decompensation
Functional diagnosis: class II*
Therapeutic diagnosis: class C†

Since no cardiac evaluation is complete without prognosis, the questions still remain to be answered: What was the President's outlook for survival had he not been assassinated? Could he have outlived the more than three remaining years of his second term of office?

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*"Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea and anginal pain."[15]

†Patients with cardiac disease whose ordinary physical activity should be moderately restricted, and whose more strenuous efforts should be discontinued."[15]

Refer to: Bruyn HB, Crocker S: Health screening and the role of nurse assistants—Medicolegal considerations in California (The Health Care Team). West J Med 128:178-184, Feb 1978

Health Screening and the Role of Nurse Assistants

Medicolegal Considerations in California

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In 1974 the California State Legislature mandated the Child Health and Disability Prevention program (CHDP), a health screening program to provide early and periodic assessments of the health status of all children who are entering first grade and all children who are Medi-Cal beneficiaries under the age of 21.

The CHDP program is an extension of the federally mandated Early, Periodic Screening, Diagnosis and Treatment (EPSDT) program that was established in 1967 under Title XIX of the Social Security Act. Under EPSDT, programs for early and periodic screenings of all Medicaid-eligible children under the age of 21 were to be established in all states. The California State Legislature adopted the CHDP program in response to the federal legislation and elected to expand the population covered by the program to all children entering the first grade.[1]

The goals of the California CHDP program are (1) to provide for the early identification and referral for treatment of children with handicapping conditions before they become chronic and irreversible damage occurs or to lessen their impact on persons so afflicted, (2) to prevent physical and mental disabilities in children and (3) to benefit the health and welfare of the citizens of California by reducing the incidence of such conditions.[1]

Extensive CHDP guidelines, delineating the scope of the program and procedures to be used, were issued in April 1975. Table 1 summarizes the tests and procedures that may be included in the health assessment or screening program for children and young adults from birth to 21 years of age. The inclusion of any one procedure or test is the decision of a physician.[2]

It is anticipated that the CHDP/EPSDT program will have far-reaching effects on preventive medical programs for children and on the health care delivery system in California. In 1974-1975 the State Department of Health determined that in California more than 330,000 children would be attending first grade and more than one million persons under 21 years of age were eligible for MediCal (the Medicaid program in California) and EPSDT in the fall of 1975. This represents a significantly large population to be screened every year under both programs. With the existing shortage of primary care physicians in many areas of the state, it is more probable that physicians will not always be available to implement the program; nurse practitioners, physician's assistants, and other paramedical personnel can and will be used to conduct the health assessment programs in many areas.

The concept of health screening is difficult for many professionals to understand or accept. It is looked upon by some as a poor quality procedure that contrasts with the traditional "complete diagnostic evaluation." It is certainly not intended to be a complete diagnostic study and in fact is intended to avoid any implication of specific diagnosis or treatment. Screening is a most important first step toward diagnosis and is very definitely not an end in itself.

According to the regulations, the CHDP pro-

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ABBREVIATIONS USED IN TEXT

CHDP = Child Health and Disability Prevention program
EPSDT = Early, Periodic Screening, Diagnosis and Treatment program

cedures and EPSDT are screening programs. Screening is defined as "the use of simple procedures to sort out from apparently well persons those who have suspected disease or abnormality and to identify those in need of more definitive study of potential physical, mental or other health problems."[3] The regulations state that all of the required procedures and tests, as listed above, can be carried out by nurse practitioners, physician's assistants, health aides and other personnel with specific training—all under the supervision of a physician who is responsible for the selection of the staff and their training or verification of their training.

While the regulations establish program standards and specify the personnel that may be used to conduct health assessments, many issues with medicolegal implications are raised. Some of these are the following:

- What are the implications of a physician delegating certain tasks?
- What is meant by supervision?
- What is the physician's responsibility for supervision of the personnel conducting the screening tests and procedures?

The medicolegal liability of nurses in health screening programs is not clear. Although the parents or the young adult client must be informed of the results of the tests conducted in the screening programs, the qualifications and limitations applicable to this information are not clear.

Physician Responsibility

The medicolegal implications of delegating certain medical acts to nonmedical personnel are brought into question. What is meant by supervision of staff members who are performing tests, and what are their responsibilities for informing the parents or the young adult client of potentially significant findings from the health assessment? These are complex questions and many are presently without answers. Medical and nurse practice acts are very general and there have been very few court cases that specifically relate to responsibilities of the physicians for the clinical activities of assistants.

Delegation

Most medical practice acts provide that no one can "diagnose, treat, operate, or prescribe" unless he or she is a licensed physician in the state. According to California laws, only licensed physicians may practice medicine and it is illegal for physicians to delegate the practice of medicine to anyone not licensed as a physician. Statutes recognize that if such activities are delegated, the physician may be aiding and abetting the illegal practice of medicine.

During the past few years, the American Medical Association, the American Hospital Association and the Department of Health, Education, and Welfare have issued statements urging state legislatures to adopt amendments to the medical practice acts which will give physicians the authority to delegate specific tasks to health personnel working under their control and supervision.[4-6] At present, physicians rely on the doctrine of "custom and usage" to delegate medical acts to nonmedical personnel. However, this is not sufficient to protect physicians from liability nor does it apply readily to innovations in the utilization of health care personnel such as nurse practitioners or physician assistants.[7]

Amendments providing for the delegation of some medical tasks had been adopted in 24 states by the end of 1972.[8] These amendments, however, fail to specify which tasks may be delegated. Most of them provide that physicians may delegate any act, task, function or service to be rendered. In California a physician may delegate certain specific tasks to physician's assistants, but no provision is made for delegation to other health care personnel. The Physician's Assistant Act includes a detailed list of tasks that may be carried out by a physician's assistant.[9]

Physicians are gradually delegating more of their work to assistants, especially where little risk to the patient is involved. While courts may consider the "customs and usages" which prevail in the medical community when determining if delegated functions are appropriate, the courts may still find physicians liable for delegation of acts to personnel who are not qualified to perform them.

Supervision

Directly related to the issue of delegation is the question of physician supervision of health personnel in screening procedures. Amendments to state medical practice acts permitting delegation

of tasks also require that these tasks be done under the "supervision and control" of a licensed physician. The term "supervision and control" is generally not defined in the laws.

The potential personal liability of the physician falls into three classes. First, the supervising physician is vicariously liable for the acts of the health personnel conducting the screening tests, under the doctrine of *respondeat superior*—which means the master is held liable for the acts of his or her servants, or employees.[10] Finally, the physician may be held liable for tasks delegated to health personnel which are beyond their experience or competence.[11]

In California the Health and Welfare Agency issued regulations for the CHDP program, which delineate the responsibilities regarding physician supervision.[2] All programs are to be conducted under the supervision of a licensed physician. "The supervising physician shall be responsible for the selection of the staff, their training or verification of their training and the general supervision of their work. . . . He shall be available either in person or by direct communication to the staff during such times as the screening is being conducted."[2]

Physician supervision of health personnel used in health programs, screening programs and indeed clinical practice provides the necessary assurance that all the personnel's activities are medically safe and proper. This supervision may be carried out on at least three different levels: "over the shoulder," on the premises of a clinic or office, and by direct communication from the physician by telephone or in writing. While "over the shoulder" or on-the-premises supervision may ensure that health personnel are adhering to medically safe and proper practices, the required supervision defeats the physician's efficiency gained through delegation of tasks. It is believed that the quality of care with supervision by a physician not on the premises can be maintained and defended if health personnel are well trained and if they have adequate written task definitions, procedures and review.[12] It is the physician's responsibility to be fully knowledgeable about these and about the qualifications of the personnel. Health personnel including nurse practitioners "can work a substantial distance from a physician but still be legally 'dependent' because their actions are subject to continuous medical review and direction."[12]

It should be noted that the term "physician supervision" of health personnel is neither defined by statute nor common law. This leaves the ". . . rendering of judicial construction of the term extremely important to the nature of the relationship between the physician and the paramedic."[13]

Informing the Client or Parent of Test Results

The relationship of physician and patient is generally one of trust and confidence, which creates a fiduciary responsibility for a physician.[14] This imposes on the physician a duty to inform the patient of unfavorable diagnosis or tests. In *Wohlgemuth vs Meyer,* the court stated that it is incumbent upon the physician to reveal all pertinent information to his or her patient, observing that a physician is required to make full and fair disclosure of "all the facts which materially affect the patient's rights and interests."[15] This duty is dictated by what is in the best interests of the patient and is measured by the standards of what a reasonable physician in the same community would disclose under the circumstances.

Under the CHDP program the screening provider must inform the parents or the young adult client of the results of the screening procedure and explain the results of the tests.[2] In addition, the regulations clearly state that the health personnel shall not represent the screening process as a complete or comprehensive examination and that no person other than a physician may make diagnostic statements based solely on the results of the screening procedures.[2] These regulations insure that the children's parents or the young adult clients are informed of the results, both favorable and unfavorable, and help to insure that there is not a misrepresentation as to the type or purpose of the screening process. Many health screening programs have provided clients with written statements defining the screening process and its limitations. These statements usually emphasize that a physician will use the results in making a diagnosis and recommending treatment.

Use of Nurses and Other Health Personnel in Screening Programs

Under the CHDP and EPSDT regulations, nurses and paramedical personnel can be used to carry out most of the tests and procedures as listed in Table 1. The roles of nurses and other health personnel are expanding as state legislatures and the medical community recognize the necessity of developing new kinds of health manpower. In

addition the reallocation of the performance of health tasks, tests and procedures to health personnel not previously permitted to do them is rapidly occurring.[12]

While it is common practice to use nursing and other health personnel to carry out the screening procedures, it is necessary to consider the medicolegal implications of using such persons in these programs. There is much discussion as to which acts done by a nurse are the practice of medicine as opposed to the practice of nursing. The role of nurses is expanding and this has enabled nurses to assume responsibilities which have been restricted to physicians in the past. A review of the literature over the past few years documents the expanded role of nurses in primary health care services and screening programs, and the overlapping functions between physicians and nurses. One of the difficult issues created by this situation is to delineate between the practice of medicine, which is strictly limited to physicians, and the practice of nursing.

TABLE 1.—*Summary of Tests and Procedures Included in CHDP Health Assessment*

Screening Evaluation of Health Status (SEHS)
- A. Historical Review
  - Brief history of pregnancy, birth and neonatal period where not already recorded.
  - Illness and hospital history when not recorded.
  - Assessment of physical growth and development.
  - Family health—history and current status.
  - Nutrition review and evaluation.
- B. Physical Examination
  - Measurement of height and weight
  - Measurement of head circumference up to one year of age.
  - Measurement of blood pressure.
  - Unclothed physical examination for obvious physical defects including skin, head, eyes, ears, nose, mouth, throat, neck, chest, abdomen, genitalia, extremities, brachial and femoral pulses. If skilled personnel are available, stethoscopic examination of heart and lungs are of course included.

Vision Screening
Hearing Screening
Assessment of General Dental Needs
Tuberculin Testing
Screening Laboratory Tests
- Tests for anemia; either hemoglobin determination or microhematocrit. These tests may be done on the clinic or office premises.
- Urine screening for sugar, protein and blood by the "dip stick" method on office or clinic premises.
- Tests for sickle cell trait, syphilis, phenylketonuria and gonorrhea may be carried out in licensed facilities when considered appropriate by the physician.
- Papanicolaou smear may be done when ordered by a physician, and a licensed laboratory is used.

Immunization Review and Update to Recommended Standards

In screening programs and clinics nurses carry out many functions that are medical acts. This issue has been addressed by many professionals and there appears to be some agreement that:

> . . . in the absence of statute, custom and usage generally will control the nature and scope of acts performed by nurses. Among the minimum requirements for a nurse's authority to perform such acts are that she proceed under the order and direction or supervision of a licensed physician and that she comprehend the cause and effect of the order.[16]

The American Medical Association Committee on Nursing issued a statement in 1970 that said, "as there is a marked overlap in the technical areas common to medical and nursing practice, the same act may be clearly the practice of medicine when performed by a physician and the practice of nursing when performed by a nurse."[17] The committee also states that the general definitions used in the state medical and nurse practice acts do not present restrictions on the growth and expansion of the scope of nursing practice.

In 1974 the California State Legislature amended the Nurse Practice Act to redefine the practice of nursing.[18] The Act provides "clear legal authority for functions and procedures which have common acceptance and usage." It also states it is the intent of the legislature "to recognize the existence of overlapping functions between physicians and nurses and to permit additional sharing of functions within organized health care systems which provide for collaboration between physicians and nurses."[18]

The above statements raise, again, important issues which have already been discussed in the context of other topics in the present review. First, what responsibilities may be delegated to a nurse and what constitutes diagnosis? Second, what is meant by supervision? Third, what are the legal liabilities of a nurse practicing in a screening program or clinic?

Delegation and Diagnosis

While nurses and other health aides may do many of the procedures and tests making up a health assessment or screening program under the supervision of a physician, their activities could be considered the practice of medicine. If screening is defined as the use of simple procedures to identify people who have suspected disease or abnormalities and the identification of those in need of more definitive study or care, this then

may be interpreted as diagnosis, which is an act restricted to licensed physicians.

The term diagnosis is defined in Section 2013 of the California Medical Practice Act as "any undertaking by any method, device or procedures whatsoever as to ascertain or establish whether or not a person is suffering from any physical, mental or nervous disorder." This definition, however, does not exist in distinguishing between those acts of a nurse that may constitute diagnosis, and therefore the practice of medicine, and those that are the practice of nursing, as defined in the Nurse Practice Act. The courts have made different interpretations of these acts.

According to Sadler some courts have held that "the nurse is properly allowed the responsibility of judging the gravity of symptoms without engaging in diagnosis. Others conclude that when a nurse evaluates a symptom and decides that no serious disease is indicated, she is diagnosing."[12] As physicians, nurses, attorneys and the courts attempt to define what is meant by diagnosis they are forced to engage in semantic games.

Two examples of this are seen in the following excerpts from Lesnik and Anderson.[16] In discussing the term diagnosis, they say:

> . . . an obligation to observe symptoms and reactions (nursing functions) seems to be intertwined inextricably with diagnosis, and the latter is generally acknowledged within the exclusive province of those who practice medicine. . . . Nevertheless, there is an area with which the nurse is charged, and that area may well be called nursing diagnosis.

Another example of efforts to skirt the legal requirement to restrict the practice of medicine to licensed physicians has been through the use of standing orders. It is a common practice in some health care clinics and screening programs for physicians to issue standing orders for use by nurses and other health personnel. While this may meet the requirement of medical supervision or direction in the absence of a physician on the premises, it raises some legal questions. Lesnick and Anderson state that "to the extent that orders constitute instructions for cases already diagnosed, such orders are valid." However, "a physician may not delegate the authority to diagnose, to treat or to prescribe. A standing order for treatment of a headache or a cold is illegal since it presupposes a prescription based on diagnosis."[16]

The California Nurse Practice Act states, in part, that nurses may carry out, according to standardized procedures, basic health care, testing and prevention techniques. It also states that nurses may provide direct patient care including but not limited to administration of medications and therapeutic agents necessary to implement a treatment regime prescribed by a physician.[18] The definitions of nursing practice would appear to be sufficiently broad as to allow the nurse to do many tasks in screening programs and health care clinics which in the past were not authorized. The revised Nurse Practices Act of California may also eliminate or at least minimize many of the issues raised about physician delegation of tasks in screening programs and clinics.

Supervision of Nurses

Closely related to delegation of tasks is the issue of supervision. As discussed in a previous section, a physician has a responsibility to supervise the health personnel to whom he or she delegates tasks and responsibilities. In most clinics and health screening programs, tests and procedures are conducted under the direction of a physician. Depending on the nature of the program, the training of the staff and the tasks to be carried out, it may or may not be required for a nurse or other health personnel to be directly supervised by a physician on the premises; availability of a physician by telephone may be sufficient. However, as Andrus and Fenley note:

> . . . delegation of tasks, whether directly or through protocols and consultation should include sufficient supervision to assure that the nurse collects pertinent data, accurately interprets the data and recognizes deviations from the normal and understands his or her limitations in diagnosis and therapy.[19]

CHDP regulations delineate those screening tests and procedures that may be done by a nurse and also those that may be done by other health personnel, including health aides and trained volunteers.[2] These regulations also state that all tests and procedures, as listed in Table 1, regardless of who does them, shall be done under the supervision of a physician. Nurses and other health personnel are specifically precluded from making any diagnostic judgments based on the results of the screening procedures by Section 6040(c) which states the supervising physician shall personally review all suspected abnormal findings and approve referrals for further diagnosis and treatment.[2] This not only insures quality control of staff performance through review by a physician but also that the program is adhering to its legal responsibilities as defined by the laws.

Liability of Nurses

Nurses are held to the standard of learning, skill and care ordinarily exercised by reasonably prudent nurses in the community or similar communities. They will be held responsible for their own acts if they fail to meet this standard of care. Nurses who supervise other health personnel may also be held liable for their negligent acts. This liability is not based on the doctrine of *respondeat superior,* but is a liability that may be incurred when a nurse may be deemed negligent "in failing to properly supervise such personnel or in delegating and assigning tasks to those who were incompetent to perform them."[20]

In most screening clinics or programs, nurses are the employees of a physician. Consequently, when a nurse carries out duties under the supervision of a physician, the boundaries of responsibility are less clearly defined: "The nurse is not completely independent, nor is she completely the agent of the physician. In the performance of a strictly nursing activity she is liable for her negligence."[20] But for those duties that are within the scope of the authority delegated to a nurse by a physician, the physician may be held liable under the doctrine of *respondeat superior.* This doctrine should act as an incentive for physicians to maintain adequate supervision of their employees and supervisees.

Explaining to Clients About Screening Program Limitations

It is important that people seen in an organized screening program understand what the limitations of such tests and procedures are. It is important to avoid in every way the impression that the screening program is a diagnostic or therapeutic program. Many persons may believe that because a few tests have been carried out and they have had a physical examination, this represents a complete or comprehensive examination. They may fail to seek medical advice or treatment for a condition not detected in the screening program because they did not understand the limitations of the procedures and tests. In addition, it is necessary that clients understand that in instances where the tests and procedures are carried out in screening programs by nurses, physician's assistants and other health personnel, these persons are not permitted by law to diagnose or treat.

To minimize any misunderstanding about a screening program, the significance of the outcomes, and who is carrying out the tests and procedures, it is recommended that a nurse explain the scope of the program and have the clients, or in the case of a child, the parents, acknowledge their understanding by signing an appropriate statement. An example of what such a statement might contain is:

> I understand that this program is for screening only and that it does not diagnose diseases. I understand further that there may be diseases not detected by these procedures or that I may receive a report indicating a possible need for medical attention which when given will not result in a specific diagnosis. Knowing these limitations of the health assessment program, I accept responsibility for any follow-up action that may be suggested or advised, and wish to have my child participate.

This may clarify the parents' or clients' expectations of the screening program and may help to minimize the liability of the screening program should a question be raised about expectations or understanding of the program.

Naturally, these suggestions are inappropriate in the situation where a physician is carrying out the entire health assessment in a clinic or private office setting. In this case, the physician will explain the findings and the need for further diagnostic study or treatment—if any.

Medicolegal Risks

The medicolegal issues regarding the uses of nurses and other health personnel in health screening programs and physician delegation of tasks and supervision of personnel are complex issues of major concern. There have been very few court cases at the appellate level which specifically relate to the legal responsibilities of the physician delegation of duties to nonphysicians and there have not been many cases of negligence against nurses practicing in clinical settings. It should be noted that many cases are settled out of court or by insurance companies (or both). It might also be noted that to date there has not been a single suit recorded against a physician assistant who was a graduate of a recognized medical school program.[11] While these may be seen as positive signs, it may be that there are few cases because the use of paramedical personnel, nurses and physician's assistants is a fairly recent development.

In his article "Recent Legal Developments Relative to Physician's Assistants and Nurse Practitioners,"[12] Blair Sadler makes a persuasive argument that the use of well-trained nurse practitioners and physician's assistants who carry out

their tasks within their capacity and under the supervision of a physician, will reduce the malpractice risk. Sadler argues that:

First, effective utilization of physician's assistants and nurse practitioners will allow the physician to concentrate on those medical procedures and judgments that only he can manage. Second, malpractice suits often result from poor patient rapport rather than negligence per se. When a patient is seen after a considerable wait, and then hurried by a harassed physician, the probability of patient dissatisfaction is magnified.[12]

Conclusions

Health screening should be clearly presented and understood to be an attempt to identify those in need of more definitive study of potential physical, mental or other health problems. No implication or expectation of a specific diagnosis, treatment or a ruling out of a possible diagnosis should be allowed.

The responsibility of a physician in a health screening program should be clear. The delegation of responsibilities by the physician to nonmedical personnel should be undertaken with great care, in writing and with demonstrable knowledge on the physician's part of the skills and limitations of those to whom such responsibility is delegated. Supervision of nonmedical personnel should also be clearly established in written form.

The charter of and expectations for a health screening program should be made clear, preferably in writing, to parents or to young adults.

The physician may not delegate the authority to diagnose, to treat or to prescribe.

The 1974 California Nurse Practice Act provides "clear legal authority for functions and procedures which have common acceptance and usage." Nurses may carry out basic health care, testing, and prevention procedures in licensed health facilities or organized health care systems.

Nurses are held to the standard of learning, skill and care exercised by a reasonable prudent nurse in the community. Nurses may be held liable for negligence on the part of personnel under their supervision. A physician may be held liable for the acts delegated to the nurse.

The Nurse Practice Act of California, while apparently illuminating many of the issues raised in the delegation of responsibility by the physician, has not yet been tested in the courts.

The prudent and effective use of nurse practitioners may reduce the malpractice risk in office, clinic or screening program.

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Information

Munchausen Syndrome Presenting as Urolithiasis

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BARON KARL FRIEDRICH HIERONYMOUS VON MUNCHAUSEN'S confabulations and peregrinations have been recorded and embellished by Rudolph Eric Raspe.[1] Allegedly, the Baron (1720-1791) traveled through the Continent and England in the late 18th century entertaining many fellow tavern dwellers with his tall tales. A syndrome of factitious illness, convincing (though often self-inflicted) signs of disease and wandering from hospital to hospital has been named after the Baron: the Munchausen syndrome.[2] Though the literature is replete with examples of this syndrome, the presenting signs and symptoms infrequently involve the urinary system. Factitious hematuria with or without the association of renal colic has been reported in ten cases,[3-8] the presentation of a "passed" synthetic renal calculus has been reported in three.[9-11] Herein we will present four additional cases and discuss some common factors shared by them and the Munchausen syndrome in general.

Reports of Cases

CASE 1. A 22-year-old white naval enlisted man was admitted with a 12-hour history of left colicky flank pain associated with smoky colored urine. He later reported pain radiating down into the left testicle with nausea, vomiting and fever. Past urological history showed a left pyelolithotomy via a transabdominal approach for an obstructing "black, radiolucent stone" two years earlier. One year before the present admission another "small black radiolucent stone" on the left side was passed spontaneously. One month before admission, studies had been done for left flank pain and a low grade fever in Vietnam and later the patient was transferred to a military hospital in the United States. The patient stated he was allergic to propoxyphene, morphine, atropine and urographic contrast material—the latter causing hypotension.

On physical examination the body temperature was 39°C (102.2°F) and pulse rate was 72. Examination of the abdomen showed pronounced left upper quadrant, left lower quadrant and left costovertebral angle tenderness; a midline abdominal scar; right lower quadrant scar; right inguinal scar, and left flank scar. The following laboratory findings were recorded: leukocyte count, 8,600; normal values for serum calcium, phophorus and uric acid; 15 to 20 red blood cells per high power field on analysis of urine. A kidney, ureter and bladder study showed no abnormalities.

Cystoscopy and left retrograde pyelogram were done and findings were normal. Urine culture from the left ureteral catheter showed no growth. Subsequent telephone conversation with personnel at a regional naval hospital showed that the patient had been discharged one day earlier, having presented with an identical symptom complex; cystoscopy and left retrograde pyelogram had been negative. Furthermore, medical records showed that he had been admitted to numerous military medical facilities in the Philippines and Vietnam for identical reasons. Communications with the military psychiatric service showed that they were not interested in his future care and he was subsequently discharged from the hospital to return to active duty.

CASE 2. A 27-year-old single French-Canadian man reported that severe right colicky flank pain lasting for two hours had occurred while he was traveling between Vancouver, British Columbia, and Portland, Oregon. Gross hematuria during evaluation was noted in the patient in the emergency room. He claimed that studies had been done one month before admission for an episode of bilateral flank pain in Montreal, where microscopic hematuria was noted. Excretory urography

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resulted in an allergic reaction which he thought had required epinephrine. In addition, 2½ weeks earlier the patient had undergone litholapaxy for bladder stones (which he thought were uric acid in composition) and bilateral retrograde pyelograms, the results of which he did not know. He also admitted to several attacks of gouty arthritis, and an elevated level of serum uric acid treated with allopurinol and sodium bicarbonate.

Pertinent physical findings showed a normal temperature, right upper quadrant abdominal tenderness and guarding, and multiple venipuncture marks of the arms. Laboratory studies gave the following findings: leukocyte count, 6,900; 20 to 30 red blood cells per high power field on analysis of urine; greater than 10^5 alpha streptococcus and neisseria resembling respiratory flora on urine culture, and no calcification shown on a kidney, ureter and bladder study.

Our suspicions were aroused because of the preceding patient and we scheduled a cystoscopy and right retrograde pyelogram. When the anesthesiologist opened the patient's mouth, he exclaimed that the buccal mucosa looked like raw hamburger, this having most likely been self-induced to produce the blood for his factitious hematuria. In retrospect it is apparent that all of the patient's urine specimens had been collected in private. Cystoscopy showed bilaterally clear efflux but an edematous and inflamed right ureteral orifice. A right retrograde pyelogram showed no abnormality. A telephone call to Vancouver General Hospital gave the information that the patient had undergone a stone basketing attempt of the distal right ureter just the preceding day. When confronted with these facts, the patient admitted that he had succeeded in traveling from South Africa to Canada, journeyed across Canada and now was in the process of migrating southward along the West Coast of the United States by frequenting many hospitals with the above history (in order to receive free lodging). He was discharged and telephone warnings about this case were made to the urology services at the University of Oregon and the University of California at San Francisco.

Case 3. A 48-year-old black man was seen in the emergency room with complaint of colicky left flank and abdominal pain, bloody urine and blood loss from the nose. He claimed to be a minister and also the president of the University of Nicaragua on a lecture tour from Mexico City to Vancouver. He stated that the previous day hospital admission had been required in Mexico City while passing two uric acid calculi, a third stone having been basketed from his distal left ureter. His past medical history was pertinent in that he claimed "factor 9 deficiency haemophilia," gout for which he was currently taking allopurinol and sodium bicarbonate, and recurrent uric acid calculi. He reported having passed six stones in the past 15 years and having several stones basketed in London 10 years ago while on a speaking tour. He claimed allergies to penicillin, morphine and iodinated contrast materials, the latter manifested by "bronchospasm and cardiac arrest."

On physical examination the patient was noted to be obese and in moderate distress with left costovertebral angle and left-sided abdominal tenderness. He was afebrile. There were bilateral anterior thigh masses which the patient claimed were silastic "pillows" placed to allow painless intramuscular injections. Pertinent laboratory data included leukocyte count, 4,800; hematocrit reading, 41 percent; blood urea nitrogen, 9 mg per 100 ml; factor 9, 100 percent activity; gross hematuria with clots on analysis of urine, and no abnormalities shown on kidney, ureter and bladder study.

On the morning after admission, while telephone calls were being made to substantiate the patient's identity, he informed the charge nurse that he had just learned that his grandmother and eight nieces and nephews had been killed in an automobile accident in Nicaragua. He then promptly disappeared down the back stairs of the hospital. Two days later a phone call was received from a hospital in Chico, California. They had admitted a patient with the same name and a similar story. The patient said he had been a patient in a Seattle hospital, but could not recall the hospital's name.

Case 4. A 33-year-old woman, having just recently arrived in Seattle from Puerto Rico, was admitted for acute onset of severe left flank pain radiating to her left lower abdomen. Urological history indicated recurrent ureteral calculi for the past 16 years. One stone in the left ureter required basketing. A right nephrectomy was done three years previously for calculi, but when inadvertently a "cancer of the kidney" was discovered at operation, the right ovary and part of the soft tissue of the right thigh were also resected. She

received postoperative radiation therapy. Additional operations included four exploratory laparotomies for bowel obstruction, cholecystectomy, appendectomy, six incisional herniorrhaphies, partial resection of the left upper arm for a malignant lesion, and numerous local excisions of sebaceous cysts. She reported having multiple allergies including intravenous pyelogram dye (which caused "shock"), meperidine, pentazocine hydrochloride, codeine and penicillin.

On physical examination, the patient was noted to be obese and afebrile. Examination of the abdomen showed moderate left costovertebral angle tenderness and a right flank scar, multiple abdominal scars and decreased bowel sounds. Surgical scars were noted on the left arm and right thigh, and there were numerous smaller scars on the patient's body. Laboratory data included leukocyte count, 4,000; hematocrit reading, 33 percent; serum calcium, 8.6 mg per 100 ml; serum uric acid, 5.5 mg per 100 ml; +1 protein and 30 red blood cells and 20 leukocytes on high power field on analysis of urine. Radiopaque densities in the region of the left kidney and midureter were noted on kidney, ureter and bladder study.

Frequent large doses of morphine were required for control of pain. Additional oblique abdominal films appeared to project the radiodensities outside of the expected course of the left collecting system. On closer examination these appeared to be calcified subcutaneous nodules located under scars, presumably self-inflicted. Also an iodohippurate sodium ^{131}I renogram and technetium 99m DMSA (2,3-dimercaptosuccinic acid) renal scan showed a normal left kidney with no evidence of obstruction of the collecting system. The body temperature was recorded at 40°C (104°F), with a corresponding pulse of 80. The temperature was taken again 10 minutes later with a nurse in attendance and was found to be 37.7°C (99.86°F); 15 minutes later it was 37°C (98.6°F). The patient discharged herself at this point stating that every other doctor had been able to help her and that we were not. She also complained that she was not getting adequate pain medication.

Two days after discharge the patient reappeared in another Seattle training hospital complaining of acute left flank pain of two hours duration with the similar allergy history and was given 10 mg of morphine for a suspected left ureteral calculus seen on the kidney, ureter and bladder study. Analysis of urine showed 40 red blood cells per high power field. She was discharged from the emergency room feeling much improved but returned four days later with the same presenting complaint. She had severe left costovertebral angle tenderness on examination, and was afebrile. Analysis of urine again showed microscopic hematuria of 20 to 30 red blood cells per high power field. She refused urethral catherization to obtain a bladder specimen and immediately left the emergency room.

Discussion

There are three characteristic features of Munchausen syndrome which differentiate it from malingering or hysteria:[5]

(1) Imposture is a characteristic. The patients' stories are frequently bizarre, describing fantastic past experiences and unusual life-styles—much as one of our patients claimed to be the president of the University of Nicaragua.

(2) Their lives have been documented as homeless by many authors. They wander either widely as our four patients did or they may stay in one general region as did the patient in the case reported by Ireland, Sapira and Templeton[4] who visited 72 hospitals in Pennsylvania, New York and New Jersey in a period of 16 years.

(3) These patients matter of factly accept certainly painful and potentially dangerous diagnostic and operative procedures in order to preserve their "cover." This masochistic, self-destructive behavior is not seen in malingerers or hysterics.

The motives of these patients are unclear. Were it not for their masochistic acceptance of dangerous procedures, one might believe them to be performing or acting to amuse and impress themselves. Some might merely desire lodging, narcotics or a haven from law enforcement authorities, and some might simply wish to outwit unsuspecting physicians. Yet most of them manifest a need for pain and perhaps even punishment. They frequently show hostile, evasive and truculent behavior on the ward, and the pronounced chronicity of their behavior suggests severe sociopathic patterns.

Patients with Munchausen syndrome presenting with factitious ureteral calculi may have some of the following common factors, which were seen in our patients: (1) They may claim a past history of radiolucent calculi with the possible association of gout or hyperuricemia (or both) for which

they are taking allopurinol and urinary alkalinizing agents. (2) They may admit to a severe allergic reaction to iodinated contrast materials. (3) They may also claim allergies to other medications including narcotics in order to lend credence to the intravenous pyelogram dye allergy or to avoid suspicion of any drug addiction. (4) A past history of urological procedures with even the presence of appropriate scars may be found supporting their history of urolithiasis. (5) Generally, the use of narcotics is sporadic and not characteristic of narcotic addiction, with withdrawal symptoms rarely occurring. (6) These patients are usually very intelligent and anticipate the questions and answers of young inexperienced and unsuspecting house officers.

The goals of physicians dealing with these patients ought to be first to make the diagnosis and then avoid any further diagnostic or surgical procedures. Psychiatric evaluation and psychotherapy are essential in trying to remedy this behavior pattern, but frequently the patients leave the hospital against advice before this can be accomplished.

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—ARNOLD G. CORAN, MD, *Ann Arbor*
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189 *An Intercity Outbreak of Meningococcal Meningitis in Adults*
PHYLLIS A. OILL, MD; ANTHONY W. CHOW, MD; RONALD R. ROBERTO, MD, and LUCIEN B. GUZE, MD

195 *Meningococcal Disease in California—Epidemiology and Management*
CHARLES JUELS, MD; FLORENCE R. MORRISON, MA; GARY D. OVERTURF, MD; RONALD R. ROBERTO, MD, and JAMES CHIN, MD

203 *Feasibility of Outpatient Self-Administration of Parenteral Antibiotics*
ANDRIS ANTONISKIS, MD; BRUCE C. ANDERSON, MD; EARL J. VAN VOLKINBURG, MD; JOANNE M. JACKSON, RN, MS, and DAVID N. GILBERT, MD

MEDICAL PROGRESS
207 *The Commitment Process for Psychiatric Patients—Changing Status in the Western States*
JAMES H. SHORE, MD

SPECIALTY CONFERENCE
212 *Management of Premature Infants With Patent Ductus Arteriosus*
Participants: T. ALLEN MERRITT, MD; LOUIS GLUCK, MD; CHARLES HIGGINS, MD; WILLIAM FRIEDMAN, MD, and WILLIAM L. NYHAN, MD, PhD
Interdepartmental Conference, Departments of Pediatrics and Radiology, University of California, San Diego, and University Hospital, San Diego

MEDICAL STAFF CONFERENCE
223 *Trace Elements* Chief Discussant: FAITH FITZGERALD, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE
228 *Pediatrics—Epitomes of Progress*

EDITORIALS
235 • *Thoughts About Geriatrics* • *Prevention of Meningococcal Disease: Practice and Prospects*
• *Public Views of NHI* • *Patent Ductus Arteriosus*

CASE REPORTS
240 *Graves Hyperthyroidism Following Myxedema in a Patient With Recurrent Carcinoma of the Colon* GERALD A. LEVINE, MD; DONALD E. WILLIAMS, MD; JEROME M. HERSHMAN, MD, and GILDON N. BEALL, MD

244 *Cirrhosis Due to Hypervitaminosis A* RICHARD R. BABB, MD, and JOHN H. KIERALDO, MD

246 *Phenytoin Overdose Kinetics*
MARK A. GILL, PharmD; JACK W. KERN, PharmD; JEANNE KANEKO, PharmD; JAMES McKEON, PharmD, and CHARLES DAVIS, MD

248 *Ventricular Tachycardia in a Young Adult With an Apical Aneurysm*
W. ALLAN EDMISTON, MD; TARO YOKOYAMA, MD; JEROME KAY, MD; MICHAEL BILITCH, MD, and FRANCIS Y. K. LAU, MD

CORRESPONDENCE
254 • *Donald Kennedy Replies* • *The Abortion Crisis—A Countervailing View*
• *The Science and the Art*

COMMENTARY
257 *Geriatrics—The Missing Discipline?* ALEX COMFORT, MB, BCh, DSc

MEDICAL EDUCATION
260 *Continuing Medical Education in Midpassage* PHIL R. MANNING, MD

SPECIAL ARTICLE
266 *Legal Implications of Physical Examinations* JEAN SPENCER FELTON, MD

274 *Articles To Read in Other Journals*

275 *Book Reviews* • *Books Received, see Advertising Page 31*

277 *In Memoriam*

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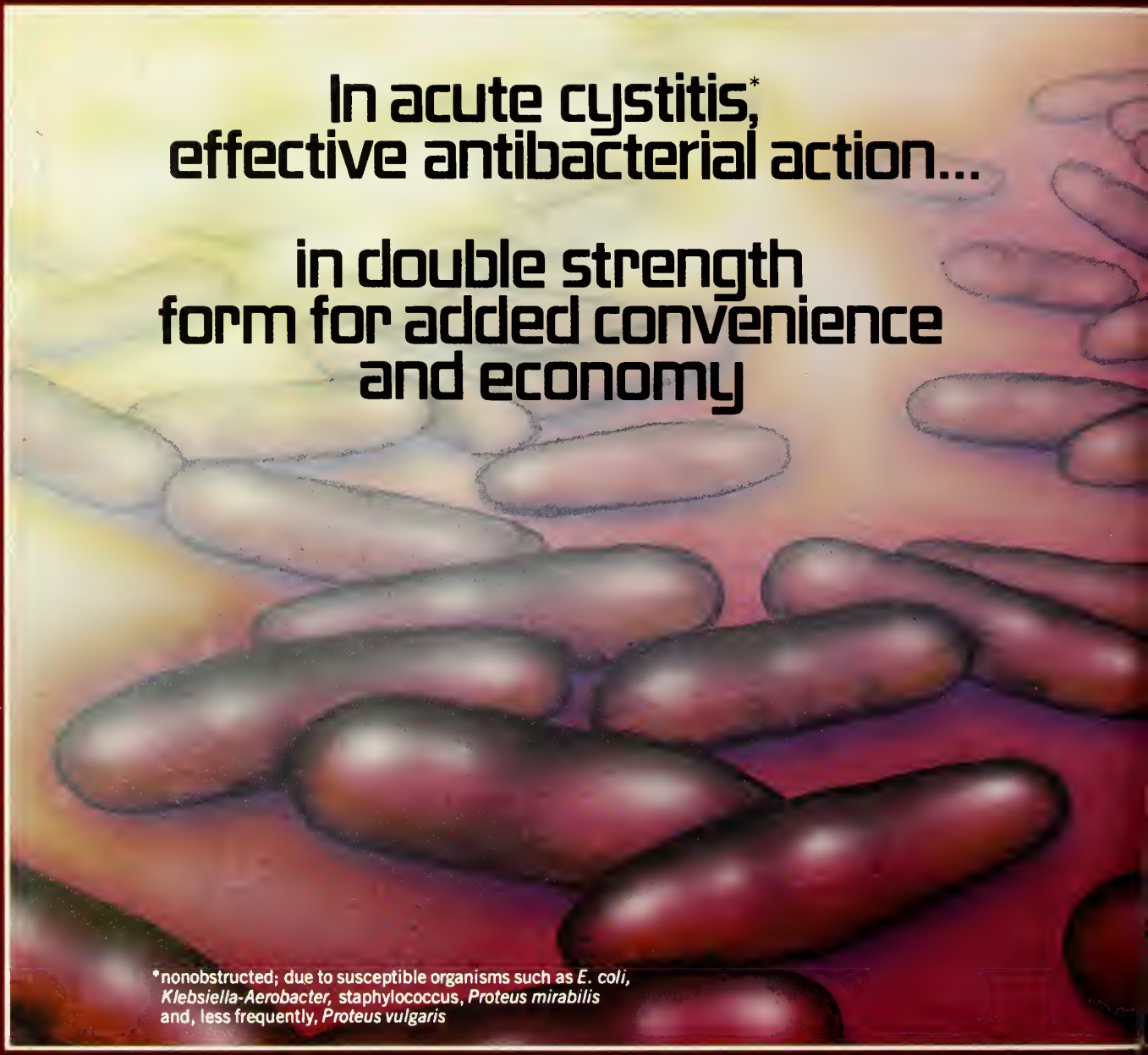
(See Advertising Page 31)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ISSN 0093-0415

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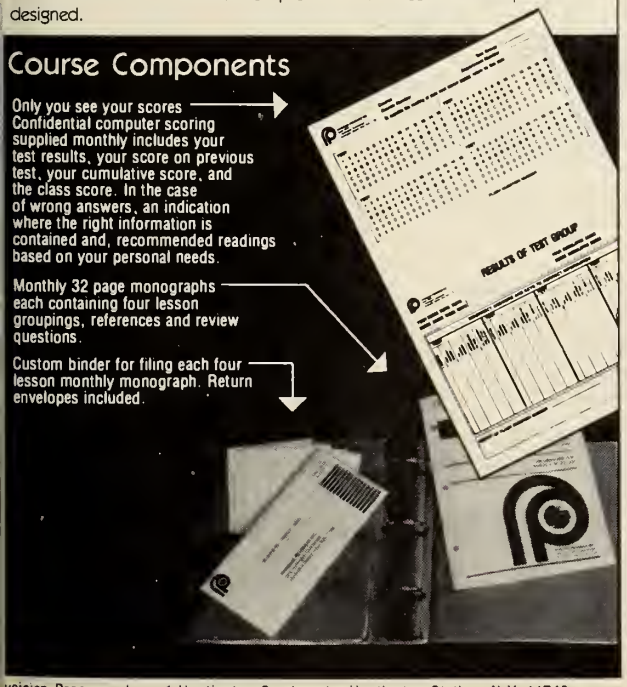

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Kaon® Elixir
(potassium gluconate)

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(potassium gluconate)

BRIEF SUMMARY
Kaon Tablets/Kaon Elixir

KAON® (potassium gluconate) TABLETS

Description: Each sugar-coated tablet supplies 5 mEq. of elemental potassium (as potassium gluconate 1.17 Gm.). Kaon Tablets are sugar coated, not enteric coated, which favors dissolution in the stomach and absorption before reaching the small intestine where the lesions with enteric potassium chloride have occurred. The sugar coating merely adds to palatability and ease of swallowing, not to delay absorption as does the enteric coating.
Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. It may be used in the treatment of cardiac arrhythmias due to digitalis intoxication.
Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.
Warning: There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides or certain other oral diuretics. These small-bowel lesions have caused obstruction, hemorrhage and perforation. Surgery was frequently required and deaths have occurred. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Coated potassium tablets should be used only when adequate dietary supplementation is not practical.
Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient and periodic ECG and/or serum potassium levels should be made. High serum concentra-

1954
1978

Time is the test of all things

ons of potassium ion may cause death through ardiac depression, arrhythmias or arrest. This rug should be used with caution in the presence f cardiac disease.

In hypokalemic states, especially in patients n a salt-free diet, hypochloremic alkalosis is a ossibility that may require chloride as well as otassium supplementation. In these circumances, Kaon (potassium gluconate) should be upplemented with chloride. Ammonium chlode is an excellent source of chloride ion (18.7 Eq. per Gram), but it should not be used in atients with hepatic cirrhosis where ammonium alts are contraindicated. Other sources for hloride are sodium chloride and Diluted ydrochloric Acid, U.S.P.

It should also be kept in mind that ammonium ycle cation exchange resin, sometimes used to eat hyperkalemia, should not be administered to patients with hepatic cirrhosis.

Adverse Reactions: Nausea, vomiting, diarrhea and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

KAON® (potassium gluconate) ELIXIR

Description: Each 15 ml. (tablespoonful) supplies 20 mEq. of elemental potassium (as potassium gluconate, 4.68 Gm.) with saccharin and aromatics. Alcohol 5%.

Indications: See Kaon Tablets.

Precautions: See Kaon Tablets.

In hypochloremic alkalosis, potassium replacement with potassium chloride (e.g., Kaochlor® 10% Liquid) may be more advantageous than with other potassium salts.

Adverse Reactions: See Kaon Tablets.

Overdosage: See Kaon Tablets.

WARREN-TEED
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Brief Summary of Prescribing Information

Actions: Pyrvinium pamoate appears to exert its anthelmintic effect by preventing the parasite from using exogenous carbohydrates. The parasite's endogenous reserves are depleted, and it dies. Povan is not appreciably absorbed from the gastrointestinal tract.

Indication: Povan is indicated for the treatment of enterobiasis.

Warnings: No animal or human reproduction studies have been performed. Therefore, the use of this drug during pregnancy requires that the potential benefits be weighed against its possible hazards to the mother and fetus.

Precautions: To forestall undue concern and help avoid accidental staining, patients and parents should be advised of the staining properties of Povan. Care should be exercised not to spill the suspension because it will stain most materials. Tablets should be swallowed whole to avoid staining of teeth. Parents and patients should be informed that pyrvinium pamoate will color the stool a bright red. This is not harmful to the patient. If emesis occurs, the vomitus will probably be colored red and will stain most materials.

Adverse Reactions: Nausea, vomiting, cramping, diarrhea, and hypersensitivity reactions (photosensitization and other allergic reactions) have been reported. The gastrointestinal reactions occur more often in older children and adults who have received large doses. Emesis is more frequently seen with Povan Suspension than with Povan Filmseals.

How Supplied: Each Povan Filmseal® contains pyrvinium pamoate equivalent to 50 mg pyrvinium, supplied in bottles of 50 (NDC 0710-0747-50; NSN 6505-00-134-1966). Povan Suspension, a pleasant-tasting, strawberry-flavored preparation containing pyrvinium pamoate equivalent to 10 mg pyrvinium per milliliter, is supplied in 2-oz bottles (NDC 0071-1254-31; NSN 6505-00-890-1093).

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BRETHINE®
terbutaline sulfate
A second wind for asthmatics
Prescribing information is summarized on the back of this page.

BRETHINE®
terbutaline sulfate

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It could mean a more active life for patients with reversible obstructive airways disease.

More effective
Brethine was more effective and longer acting than metaproterenol in a study of five patients with exercise-induced asthma.

Brethine has been shown to be highly effective alone and in combination with theophylline.

And Brethine has been shown to be twice as effective as ephedrine.

Long acting
Effect may last from 6 to 8 hours. One tablet at bedtime, upon arising and at midafternoon should keep patients breathing comfortably.

Minimal cardiac effect
Brethine produces proportionally greater changes in pulmonary function than in heart rate or blood pressure.

Tablets of 2.5 mg and 5 mg.
Some patients may experience mild hand tremor or "shakiness" when Brethine therapy is initiated. This may be minimized by starting patients with 2.5 mg doses.

Brethine®, brand of terbutaline sulfate, Tablets 5 mg., Tablets 2.5 mg. *Before prescribing or administering, please consult complete product information, a summary of which follows.*

Tablets contain 5 mg (equivalent to 4.1 mg of free base) or 2.5 mg (equivalent to 2.05 mg of free base) of Brethine, brand of terbutaline sulfate

Indications: As a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Contraindications: Known hypersensitivity to sympathomimetic amines.

Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child.

Usage in Pediatrics: Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, and hyperthyroidism. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias. Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy.

Adverse Reactions: Commonly observed side effects include nervousness and tremor. Other reported reactions include headache, increased heart rate, palpitations, drowsiness, nausea, vomiting, and sweating. These reactions are generally transient in nature, usually do not require treatment, and appear to diminish in frequency with continued therapy. In general, all the side effects observed are characteristic of those commonly seen with sympathomimetic amines.

How Supplied: Round, scored, white tablets of 5 mg in bottles of 100 and 1,000 and Unit Dose Packages of 100; oval, scored, white tablets of 2.5 mg in bottles of 100.
(B) 98-146-060-E (Rev. 4/76)667004 C76-12

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BR1282C

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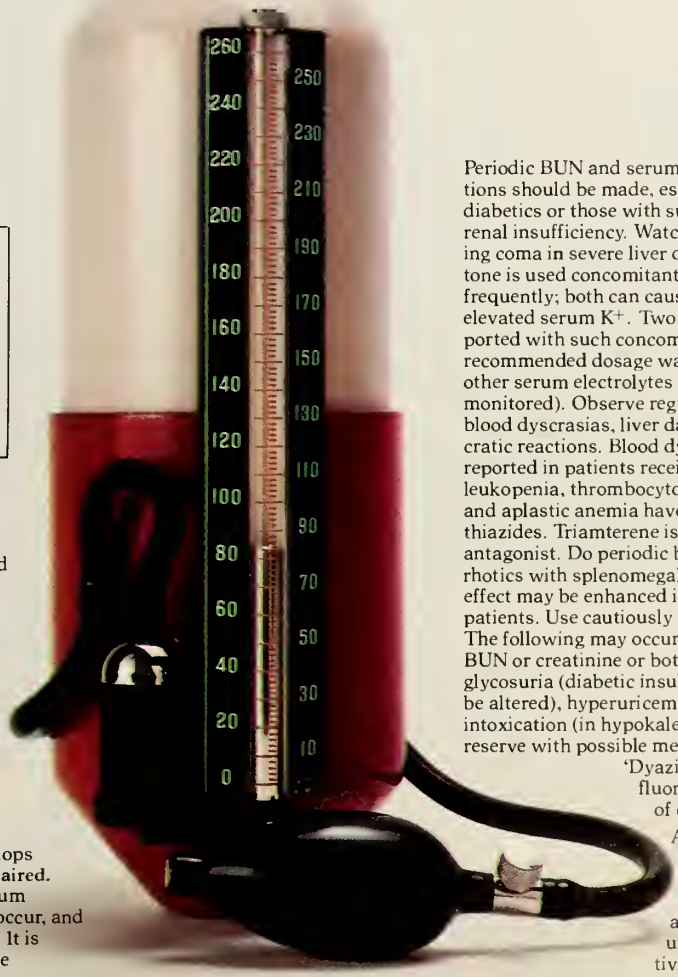

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

FOR LONG-TERM CONTROL OF HYPERTENSION.* SERUM K^+ AND BUN SHOULD BE CHECKED PERIODICALLY. (SEE WARNINGS SECTION.)

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For full details on adverse reactions, warnings, and precautions, see brief summary of the prescribing information on last page of this advertisement.

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Hypertension

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Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potentia benefits outweigh the potential risk to mother and fe *Usage in Children:* No clinical experience is availabl with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidin hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressu and associated subjective symptoms such as nervou ness, agitation, and headache. Patients should be instructed not to discontinue therapy without consul their physician. Rare instances of hypertensive ence lopathy and death have been recorded after cessatic of clonidine hydrochloride therapy. A causal relation ship has not been established in these cases. It has been demonstrated that an excessive rise in blood p sure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machir or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects alcohol, barbiturates and other sedatives. Like any c agent lowering blood pressure, clonidine hydrochlor should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochlo should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-relate abnormal ophthalmologic findings have been record with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increa in the incidence and severity of spontaneously occu ring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions ar dry mouth, drowsiness and sedation. Constipation, dizziness, headache, end fatigue have been reporte Generally these effects tend to diminish with contin therapy. The following reactions have been associat with the drug, some of them rarely. (In some instanc an exact causal relationship has not been establish These include: Anorexia, malaise, nausea, vomiting parotid pain, mild transient abnormalities in liver fu tion tests; one report of possible drug-induced hep titis without icterus and hyperbilirubinemia in a pat receiving clonidine hydrochloride, chlorthalidone, a papaverine hydrochloride. Weight gain, transient el tion of blood glucose, or serum creatine phosphoki congestive heart failure, Raynaud's phenomenon; v dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and m depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associate with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, esymptomatic electrocardiographic abnormalities manifested es Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, som lence, diminished or absent reflexes and vomiting f lowed the accidental ingestion of Catapres (clonidi hydrochloride) by several children from 19 months t 5 years of age. Gastric lavage and administration of analeptic end vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all e fects of Catapres (clonidine hydrochloride) overdos.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 10 and 1000.

For complete details, please see full prescribing information.

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THE WESTERN
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Refer to: Oill PA, Chow AW, Roberto RR, et al: An intercity outbreak of meningococcal meningitis in adults. West J Med 128:189-194, Mar 1978

An Intercity Outbreak of Meningococcal Meningitis in Adults

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An intercity outbreak of meningococcal meningitis occurred in five adults, with the acute onset of symptoms developing in two of the patients after they returned to Los Angeles from the San Francisco Bay area. The secondary attack rate was 36.4 percent in this entirely adult household. The authors review reports of secondary cases in civilian epidemics, as well as recommendations for chemoprophylaxis in household contacts.

AN INTERCITY OUTBREAK of meningococcal meningitis occurred in five adults between April 1 and April 13, 1974 (Table 1). Two patients from the Los Angeles area (Lawndale) admitted to Harbor General Hospital with meningitis said they had visited a friend in the San Francisco Bay area (Mountain View) who also had meningitis. Further investigation showed that an unusual civilian outbreak of meningitis due to a group B strain of Neisseria meningitidis had occurred. The patient in the index case was from Mountain View and four secondary cases resulted from short-term exposure to this patient. In two patients the acute onset of symptoms developed after they returned to the Los Angeles area from Mountain View. We report an account of this intercity outbreak, review the reports of secondary cases in civilian epidemics and discuss the recommendations for chemoprophylaxis in household contacts.

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Epidemiologic and Laboratory Investigations

On April 10 a case of meningococcal meningitis in a patient admitted to Stanford University Hospital was reported to the California Department of Health and it was noted that there was a possibly associated case in a patient in another hospital. The Los Angeles Health Department was notified that contacts of these two patients were in Los Angeles and one had been admitted to Harbor General Hospital. The following series of events was then elucidated (see Table 1). In Mountain View, a community near San Francisco, a household with seven male occupants (three

slept in bedroom A and four in bedroom B) reported that several members had an influenza-like illness before the outbreak of meningitis. On March 28 four men from Lawndale (including patients 4 and 5) traveled to Mountain View and slept in the household (bedroom B) on March 29 and 30, returning to the Los Angeles area on April 1. Patient 1 (index case), who slept in bedroom A, became acutely ill on March 31. A friend (patient 2), who had visited the household daily, slept at the Mountain View house (bedroom B) that night, actually staying up most of the evening to care for the sick patient (index case). On April 1, the index case patient was admitted to Chope Community Hospital, San Mateo, with meningitis. The men from Lawndale were aware before they returned home that meningitis had been diagnosed in their friend. In patient 2, arthralgias and myalgias developed on April 4, and he was admitted to Stanford University Hospital on April 7 with meningitis. At Harbor General Hospital a patient (patient 4) was admitted with meningitis on the morning of April 8. History from the persons accompanying the latter patient showed that a friend (index case) recently visited by the Harbor General Hospital patient was admitted to hospital in the San Francisco area for meningitis. The physicians at Harbor General Hospital, suspecting meningococcal disease, suggested that any person sleeping in the household of the patient (patient 4) come to the hospital for evaluation. Three persons came to Harbor General Hospital on the evening of April 8 where findings on examination were within normal limits and nasopharyngeal cultures were obtained. On April 9 one of these persons (patient 5) was admitted to Harbor General Hospital with meningitis.

The Santa Clara Health Department had dispatched a public health nurse to the Mountain View household to evaluate the situation, obtain cultures and arrange for chemoprophylaxis. On April 18, patient 3 (slept in bedroom B) was admitted to Santa Clara Valley Medical Center with meningitis. When the Mountain View residence was visited on April 12 by the public health nurse, he had been absent and no one had mentioned him.

In Los Angeles a contact tracing team went to the residence of patient 4 and obtained nasopharyngeal cultures from 23 persons who lived in that residence or who had had close contact with the patient. Rifampin, 600 mg per day for four days, was administered after cultures were obtained. All nasopharyngeal cultures taken by this team were negative for Neisseria meningitidis. However, there was a positive nasopharyngeal culture from patient 5 after he was admitted to Harbor General Hospital with meningitis. He was one of the persons who had come to Harbor General Hospital on the evening of April 8.

A total of four persons who slept in the Mountain View residence while the index case patient was ill contracted meningococcal meningitis. In none of the 23 household contacts of the secondary case patients from Lawndale (patients 4 and 5) did meningococcal disease develop following exposure in Lawndale. Similarly, meningococcal disease developed in none of the household contacts of patient 2 in Mountain View at a separate

TABLE 1.—*Summary of Cases in Mountain View-Lawndale Meningococcal Outbreak*

Patient	*Age*	*Residence*	*Date Exposed**	*Date Onset Acute Symptoms*	*Date Admitted to Hospital*	*Hospital*	*CSF Smear*	*CSF Culture*	*Other Positive Cultures*
1	17	Mountain View	Index case	3/31	4/1	Chope Community Hospital, San Mateo	Positive	Neisseria meningitidis group B	Blood
2	39	Mountain View	3/31 (daily visits before)	4/4	4/7	Stanford University Hospital	Positive	Neisseria meningitidis group B	Blood
3	18	Mountain View	Through 4/18	4/17	4/18	Santa Clara Valley Medical Center	Positive	Neisseria meningitidis group B	..
4	22	Lawndale	3/29-3/30	4/7	4/8	Harbor General Hospital	Positive	Negative†	..
5	19	Lawndale	3/29-3/30	4/9	4/9	Harbor General Hospital	Positive	Neisseria meningitidis group B	Nasopharynx

CSF = cerebrospinal fluid

*Dates include nights slept at household when index case patient was present.
†Patient received antibiotics before admission.

address. All persons involved in this outbreak were monolingual immigrants recently arrived from Mexico.

All isolates of Neisseria meningitidis recovered were submitted to the California State Department of Public Health Laboratory for confirmation. All were identified as group B Neisseria meningitidis by biochemical tests and slide agglutination with Neisseria Research Laboratory (NRL) group specific antisera. Minimal inhibitory concentrations to sulfonamide and penicillin were 8.0 μg per ml and 0.03 μg per ml, respectively.

Nasopharyngeal cultures for Neisseria meningitidis among household contacts of patients 4 and 5 in Lawndale were all negative. Contact tracing of household contacts in Mountain View for nasopharyngeal cultures and serological studies were unsuccessful.

Discussion

This meningococcal meningitis outbreak is of interest for a number of reasons. It is an outbreak involving two urban areas. Greenfield and Feldman[1] brought attention to the possible widespread dissemination of meningococcus associated with isolated cases in urban areas and today, with the ease of long distance travel, it is not surprising that persons may be exposed to an infectious process and travel to another area before symptoms develop. Certainly this is not uncommonly encountered with international travelers, and being aware that meningococcal disease can also be involved in this process, physicians should direct attention beyond the immediate family to widening circles of contact.

This outbreak occurred among adults exclusively. The report by Young and co-workers[2] of meningitis involving adults on one floor of a nursing home is the only other instance, to our knowledge, of a civilian epidemic of meningococcal disease involving adults solely. The peak incidence of meningococcal meningitis during endemic periods occurs in patients between 6 months and 5 years of age, with a second smaller increase due almost entirely to cases of meningococcal disease among military recruits.[3,4] During civilian epidemics the very young typically have higher attack rates than older age groups.[5,6] There were no children living in the Mountain View and Lawndale households and the adult spread of this disease most probably is related primarily to overcrowding.[7-9] Both Kaiser and co-workers[9] and Munford and associates[10] showed the importance of overcrowding in the civilian spread of meningococcal disease. A significant association was found between the total number of occupants in the household and the proportion of contacts infected. In both studies, the rates of infection among contacts who slept in the same room as the index patient and those who did not were identical, suggesting that closeness of sleeping contact may be less important a factor in determining the risk of infection to household members than is the total number of members in the same household, and the age of the index case patient.

Whether the high attack rate in this all male population is related to the sex of the contacts is speculative. In the Sao Paulo epidemic, attack rates were significantly greater for men than for women aged 20 to 24 years in both preepidemic and epidemic years.[11] Higher rates for young men have been noted in other epidemics.[7,12-14] One explanation for the higher rates for young civilian men than for women is the greater contact that young men might have with military friends or situations. We could not ascertain any evidence in our outbreak to support this argument, and neither could the investigators of the Sao Paulo, Brazil, epidemic.[11]

The secondary attack rate of 36.3 percent (four of 11 contacts) in this outbreak seems unusually high. It has been stated that multiple cases in households are uncommon and, although secondary attack rates in homes are difficult to calculate, rates varying from 0 to 5 percent have been reported.[5] However, secondary case rates have been approached differently by various authors. It appears that there are three distinct ways of evaluating secondary cases. The first method is by calculating the number of households with second or third cases in relation to the total number of households with cases of meningitis (Table 2, column A). Viewed in this manner, Norton[12] reported the secondary rate in the Detroit epidemic of 1929 to be 3.6 percent, or 34 out of 944 households. Foster and associates,[8] in reviewing their experience in Jacksonville, Florida, noted that two of 13 families (15.4 percent) had more than one case of meningitis. Extrapolation of the data from Kaiser and associates[9] and Munford and co-workers[10] shows secondary household attack rates of 27.3 percent and 47.3 percent, respectively. Leedom and co-workers[15] reported multiple cases to have oc-

curred among ten of 290 families at risk (3.4 percent) in Los Angeles County during a 36 month period.

Second, secondary attack rates have been calculated by noting the number of second (or third) cases reported from households in which one case had already occurred and relating this to the total number of cases reported during the study period (see Table 2, column B). Norton,[12] evaluating his data in this manner, found that of 1,272 cases there were 46 second cases (3.6 percent) from households in which one case had already occurred. Among the first 127 cases of meningococcal meningitis in the Indianapolis epidemic of 1929 to 1930, Lee[14] found that there were 29 (22.8 percent) with two or more cases in one family. In the more recent epidemic in Sao Paulo, Munford and associates[10] found the secondary case rate (excluding eight co-primary case pairs) was 18 second cases for 1,152 first cases, or 1.6 percent. These authors mentioned that the frequency of second cases in their study was lower than previously reported from epidemics of meningococcal disease, and that their method of discovering addresses probably underestimated the frequency of secondary cases.

Last, secondary attack rates have been calculated by noting the number of second cases in relation to the total number of contacts of the patient in the primary case (Table 2, column C). Contacts are defined as persons living in the same household or persons who frequently sleep and eat in the same dwelling as the index case patient. A report in 1928 by Hoyne and McEnery[16] alerted physicians to multiple cases of meningococcal disease within households. Two secondary cases occurred in a family of eight following identification of the index case for a calculated attack rate of 28.6 percent (two of seven contacts). Norton[12] noted that there were 46 secondary cases among 6,416 contacts (0.7 percent). In an extensive evaluation of 9,668 contacts of 5,885 primary case patients in the Chile epidemic (1941 to 1942), Pizzi[7] found an overall attack rate of 2.6 percent (247 secondary cases). Calculation of the data presented by Foster and co-workers[8] of multiple cases in two households shows a secondary rate of 40 percent (two of five contacts) and 20 percent (two of ten contacts), respectively. Kaiser and co-workers[9] from Florida found that five of 85 close contacts (5.9 percent) contracted meningococcal disease. In their study, if one looks at household contacts only (excluding a day-care nursery), then four secondary cases occurred out of 71 contacts for a rate of 5.6 percent. It is in this latter manner that we have calculated an attack rate of 36.4 percent, with four secondary cases of meningococcal disease occurring in 11 contacts of the index case.

It is difficult to compare the risk to particular household contacts of patients with meningococcal meningitis by using diverse means of generating secondary attack rates. It is the third method of evaluation cited above that probably most closely approaches the attack rate for close contacts. However, the studies are too small and attack rates are too varied (0.7 percent to 40 percent) to yield useful information regarding the risk of contacting meningococcal disease for family members in a particular household. Lee-

TABLE 2.—*Summary of Secondary Cases in Civilian Meningococcal Outbreaks*

Author	*A* *Number of Households With Second Cases/Total Number of Households*	*B* *Number of Secondary Cases in Household With Primary Case/Total Number of Primary Cases*	*C* *Number of Secondary Cases/Number of Contacts of Primary Case*
Hoyne and McEnery[16]	NA	NA	2/7 (28.6%)
Norton[12]	34/944* (3.6%)	46/1,272 (3.6%)	46/6,416 (0.7%)
Lee[14]	NA	29/127 (22.8%)	NA
Pizzi[7]	NA	NA	247/9,668 (2.6%)
Foster, et al[8]	2/13 (15.4%)	NA	Family 1—2/5* (40%) Family 2—2/10* (20%)
Leedom, et al[15]	10/290 (3.4%)	NA	NA
Kaiser, et al[9]	3/11* (27.3%)	NA	4/71* (5.6%)
Munford, et al[10]	26/55* (47.3%)	18/1,152 (1.6%)	NA
Oill, et al	NA	NA	4/11 (36.4%)

NA = not available

*Calculated from published data

dom and associates,[15] concerned with this issue, calculated the average number of persons residing in the same household of each patient with meningitis, based on an unselected sample of 152 of 290 (52.4 percent) families. When this figure was used to estimate the population at risk, the risk of multiple cases among household contacts of patients with meningococcal disease was about 992 per 100,000 as contrasted with the average incidence in Los Angeles County during the reported period of time (1963 through 1965) of 2.09 per 100,000. These authors make the point that this incidence would indicate a 457-fold increase in risk for household members. Nevertheless, more specific data must be generated regarding the risk to household members before the actual secondary family attack rate can be known.

The question of household risk has implications for a clinician faced with a family in which there is a case of meningococcal meningitis. Since 23 percent of case isolates from the United States recently studied at the Center for Disease Control were sulfa-resistant, and all were sensitive to rifampin, administration of rifampin is recommended as prophylaxis for family contacts of persons with meningococcal meningitis, unless the infecting strain is known to be sensitive to 10 μg per ml of sulfadiazine.[17] However, rifampin-resistant mutants have emerged,[18-20] and a secondary case of meningococcal meningitis in a family following rifampin prophylaxis has been reported.[21] Minocycline, although effective in reducing the carrier rate,[19] has considerable side effects associated with its use.[22,23] Combination therapy with rifampin and minocycline had its first trial in naval recruits with good results and few side effects.[24] However, in a study of Brazilian families, Munford and associates[25] found that although there was eradication of the organism in all carriers treated, there were significant side effects in 33 percent of the subjects. So it appears that a fully efficacious chemoprophylactic agent is not yet available; because of this, Artenstein[26] has suggested that if the organism is sulfonamide-resistant, or if no data are available, antibiotic prophylaxis is not recommended. However, a recent report from the Meningococcal Surveillance Group[27] stated that the need for prophylactic drugs for household contacts was supported by their data which showed an attack rate among household contacts to be 500 to 800 times greater than that determined for the general population. Additionally, their data suggest that an appropriately chosen prophylactic agent is probably effective in reducing this risk, and they recommend antibiotic prophylaxis for household contacts.

Polysaccharide vaccines effective against meningococcal serogroups A and C are now licensed in the United States and are available in monovalent and bivalent forms.[27] After administration, about a week is required for adequate antibody response to develop. Since about half the secondary cases of meningococcal disease in household contacts occur more than five days after the primary case, vaccination may be effective if the etiologic meningococcus is of group A or C. Vaccination is, therefore, recommended by some as an adjunct to chemoprophylaxis.[27] It should be noted, however, that the effectiveness of this approach has not been established, and that vaccine prophylaxis may provide little or no added protection over prompt rifampin prophylaxis. Additionally, serogroup B strains cause most civilian cases[27] and no satisfactory group B polysaccharide vaccine is yet available.

In our study, all available contacts to the index case patient in Mountain View and contacts of the secondary case patient in Lawndale were treated with rifampin. None of the contact cultures were positive for Neisseria meningitidis except for the patient (patient 5) admitted to hospital with meningitis. Until more definitive secondary attack rates can be ascertained, it appears that household contacts are at higher risk and should receive chemoprophylaxis with rifampin. Although primary attention has been directed towards the younger adult contacts in the past, our experience suggests that adult contacts under crowded situations may be similarly at risk. Finally, since no drug is completely effective for chemoprophylaxis, close medical observation remains an important factor in management of household and intimate contacts to meningococcal disease.

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Esophageal Pain Misdiagnosed as Angina Pectoris

A PATIENT may say that he or she has pain in the chest and this pain may be described as similar to the pain of angina pectoris. . . . Physicians may do a great disservice to their patients if they do not clearly define the nature of chest pain. Angina pectoris is, of course, typically caused by myocardial ischemia and is a deep, frightening, sometimes crushing type of pain in the chest which may radiate to the jaw, to the shoulders or down the arm. Esophageal pain is extremely similar in its descriptions and . . . in its radiation. The only way we can really distinguish the one from the other is by noting the associations. The situation arising from the esophagus and causing symptoms is usually associated, at some point or other in the history, with dysphagia. The pain of heart disease is usually, but not always, associated with activity; it may be associated with eating. . . . With these associations we can distinguish one from the other and it is extremely important to do so. It would be a great disservice if a patient has myocardial ischemia and we treat it lightly. . . . We do a patient just as great a disservice if esophageal spasm is the problem and we treat it too seriously by calling it angina pectoris. There may be as many lives being ruined in the social and personal sense by having a condition misdiagnosed as angina pectoris as there are lives threatened by a failure to diagnose angina pectoris.

—ALASTAIR M. CONNELL, MD, *Cincinnati*

Extracted from *Audio-Digest Internal Medicine*, Vol. 24, No. 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Juels C, Morrison FR, Overturf GD, et al: Meningococcal disease in California—Epidemiology and management. West J Med 128:195-202, Mar 1978

Meningococcal Disease in California

Epidemiology and Management

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Between 1969 and 1975 in California, 1,953 cases of meningococcal disease were reported. For cases reported in 1973, 1974 and 1975, detailed information about chemoprophylaxis of cases and contacts was obtained in addition to demographic and laboratory data. A review of data for the seven years showed a reduction in the case rate from 2.6 to 0.6 per 100,000 population, but this drop was due primarily to a very substantial decline in the military rate from 35.7 to 1.8 per 100,000 population. No reduction was apparent in the case fatality rate. Five groups of associated meningococcal disease cases were identified for a total of nine secondary or coprimary cases among 862 household contacts. Associated cases occurred in 10.4 per 1,000 household contacts—a rate several hundred times greater than that for the general population.

The study findings indicate that many physicians are unaware of the following: (1) nonhousehold contacts are at little or no risk of contracting meningococcal disease; (2) prophylaxis should be offered only *to household or intimate contacts immediately upon identification of an index case without waiting for test results for meningococcal carriage; (3) valid medical and epidemiologic indications exist for administering prophylaxis to household contacts who are culture negative as well as those who are culture positive; (4) the current drug of choice for prophylaxis is rifampin, but since no drug is completely effective, close medical observation remains the most important factor in the management of household or intimate contacts to meningococcal disease.*

OVER THE PAST 40 YEARS, the epidemiologic features of meningococcal disease in California have changed, as have the prevailing meningococcal serotypes and their antibiotic sensitivities. The incidence of meningococcal disease has fallen to a record low. Still, meningococcal illness retains its significance as a public health problem because of the high case fatality rate and the potential for extensive outbreaks. Even now when group A meningococcal disease has been virtually absent from California for over a decade, reappearances of this serotype may be expected based on experience in other parts of the world.

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Submitted August 10, 1977.

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Efforts to control meningococcal disease have focused on the use of antibiotic prophylaxis for household contacts because the incidence of meningococcal infections in these contacts greatly exceeds the incidence in the population at large. Effective vaccines against groups A and C meningococci have been used successfully in military populations but their effectiveness in children has not yet been established.

This study was made to review the current management of meningococcal disease in California: it is based on cases of meningococcal disease reported in California between 1969 and 1975, and on detailed follow-up reports received by the Department of Health since 1973.

Methods and Materials

The California State Department of Health has maintained a communicable disease reporting system for meningococcal disease since 1912. For the purposes of this study a case was defined as (1) a patient with clinical and laboratory findings consistent with meningococcal meningitis, meningococcemia, or both, (2) a patient who, in his physician's opinion, has meningococcal meningitis, meningococcemia, or both, regardless of laboratory confirmation, (3) laboratory report of a patient whose blood or spinal fluid has yielded meningococcal organisms on culture, (4) a death certificate that states that the underlying cause of death was meningococcal disease.

The amount of information obtained on each case has varied over the years. For cases reported between 1969 and 1972 only Confidential Morbidity Report cards with the following items of information were available: name; address; ethnic origin; sex; age; birthdate; disease suspected; dates of onset, diagnosis and death, and physician or hospital making the report. For cases reported between 1973 and 1975, these additional items were requested on a special follow-up report: date of admission to hospital; name of attending physician; military status; serotype of meningococcus isolated; source of isolate; organism sensitivity to sulfadiazine, and final diagnosis. Information requested for case contacts was age; sex; relationship to person in case; type of contact (household or nonhousehold); preventive measures applied to contacts (results of meningococcal throat cultures if taken, and type of antibiotic chemoprophylaxis if given); occurrence of meningococcal disease in contacts and date of onset.

TABLE 1.—*Reported Cases of Meningococcal Disease by Military Status* in California, 1969-1975*

	Total	Civilian	Military	Military Dependent	Unknown
	Number				
1969	515	364†	129	16†	22
1970	420	238	144	15	23
1971	450	298	132	14	6
1972	183	158	19	6	..
1973	164	150	8	6	..
1974	102	91	5	6	..
1975	119	110	5	4	..
	*Rate**				
1969	2.6	1.9	35.7	..	..
1970	2.1	1.2	41.6	..	..
1971	2.2	1.5	41.8	..	..
1972	0.9	0.8	6.3	..	..
1973	0.8	0.7	2.8	..	..
1974	0.5	0.4	1.8	..	..
1975	0.6	0.5	1.8	..	..

*Rates are per 100,000 population.

†1969 civilian cases include 16 cases among military dependents.

Source: State of California, Department of Finance, Population Research Unit, and State of California, Department of Health, Morbidity Records.

Cases which first came to attention by either death certificate or laboratory report were added to the file and the additional epidemiologic information desired was obtained wherever possible. Local health departments submitted detailed follow-up reports on two thirds of cases reported between 1973 and 1975.

The Microbial Diseases Laboratory of the California State Department of Health provides serotyping services for meningococcal isolates. After serotyping, isolates are forwarded to the Center for Disease Control (CDC) where antibiotic sensitivity is determined. Specimens, however, are not obtained from all cases: the laboratory receives specimens from approximately 15 percent to 20 percent of cases, and the results of tests done for these cases were examined along with comparative data on all isolates received by CDC.

Results

Reported Cases

Reported cases of meningococcal meningitis have declined since 1969 in both civilian and military populations (Table 1).* While 515 cases were reported in 1969, only 119 cases were reported in 1975. Military cases made up 28 percent of all cases in 1969 but constituted less than 8 percent of the total in 1975. In 1969 the rate

*Statistical assistance was given by Mrs. June Browne, Associate Public Health Statistician.

for the civilian population was 1.9 per 100,000 and in 1975 it was 0.5 per 100,000; however, a great drop in rates is noticeable for military cases during this time—from 35.7 in 1969 to 1.8 per 100,000 in 1975. Almost half of meningococcal disease cases occur in infants and children under the age of 5 and substantial declines also occurred in those groups: age-specific rates fell from 19.1 per 100,000 in 1969 to 4.9 in 1974 in those less than 1 year old and from 6.6 to 1.9 in those 1 to 4 years old (Figure 1).

Ethnic Group

An examination of attack rates by race showed that blacks were at higher risk than whites. The rate of meningococcal infections for blacks in 1970 was 2.9/100,000 compared with 2.0/100,000 for whites and 1.6/100,000 for other races. The average attack rate for the years 1969 through 1971 was 3.6/100,000 for blacks, while the rate was 2.0/100,000 for whites and other races. (Rates for each race have not been calculated for later years because reliable estimates are not available for the California population by race in intercensal years).

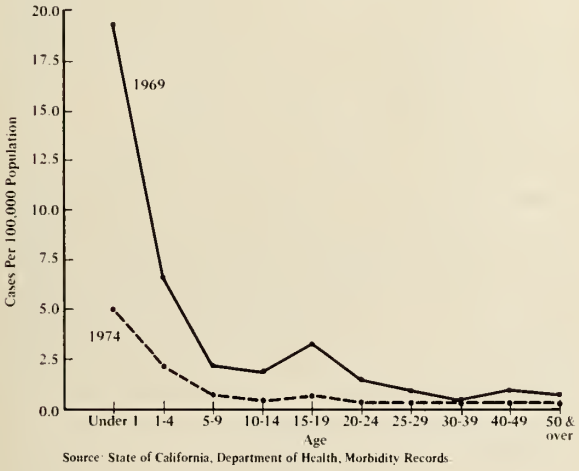

Figure 1.—Age-specific case rates of meningococcal disease in years of high and low incidence in California, 1969 and 1974.

Seasonal Distribution

Meningococcal disease in California occurs more frequently in the winter and early spring. For 1969 through 1975 combined, 55.5 percent of cases occurred between December and April.

Case Fatality Rate and Type of Disease

Case fatality rates for all types of meningococcal disease ranged from 12 percent to 21 percent between 1969 and 1975. Among civilians the range was 13 percent to 22 percent for the same period (Table 2). There was no substantial decrease from earlier years: in the previous decade case fatality rates varied between 16 percent and 21 percent. Fatality rates for whites and blacks were similar. Rates for other races seemed to be lower but the number of cases and deaths were so small that no firm conclusion was possible.

In each year meningococcal meningitis was reported at least 6 times as often as meningococcemia without meningitis and 36 times as often as meningococcemia with meningitis (Table 2). Death occurred more frequently with the diagnosis of meningococcemia without meningitis; for the seven years 1969 through 1975 the meningococcemia case fatality rate was 42 percent com-

TABLE 2.—*Reported Civilian Cases, Deaths and Case Fatality Rates* of Meningococcal Disease by Diagnosis in California, 1969-1975*

				DIAGNOSIS								
	Total			Meningococcal Meningitis			Meningococcemia			Both Meningococcemia and Meningococcal Meningitis		
Year	Cases	Deaths	Case Fatality Rate*	Cases	Deaths	Case Fatality Rate*	Cases	Deaths	Case Fatality Rate*	Cases	Deaths	Case Fatality Rate*
1969	364†	62	17.0	320	45	14.1	43	17	39.5	1	..	..
1970	238	49	20.6	197	32	16.2	32	14	43.8	9	3	‡
1971	298	38	12.6	257	23	8.9	40	15	37.5	1	..	..
1972	158	35	22.2	129	20	15.5	25	15	60.0	4	..	..
1973	150	30	20.0	118	17	14.4	23	9	39.1	9	4	‡
1974	91	17	18.7	76	12	15.8	9	3	‡	6	2	‡
1975	110	20	18.2	84	10	11.9	22	8	36.4	4	2	‡
All years ..	1409	251	17.8	1181	159	13.5	194	81	41.8	31	11	35.5

*Case fatality rates are deaths per 100 cases.
†1969 civilian cases include 16 cases among military dependents.
‡Rates not calculated for less than 10 cases.
Source: State of California, Department of Health, Morbidity Records.

TABLE 3.—*Contacts to Cases of Meningococcal Disease by Type of Chemoprophylaxis in California, 1973-1975*

	Total		Household Contacts						Non-Household Contacts					
			1973		1974		1975		1973		1974		1975	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Households	235	100	96	100	56	100	83	100	235	100	96	100	56	100	83	100
Households with contacts	195	83	76	79	48	86	71	86	79	34	28	29	31	55	20	24
Contacts	862	100	311	100	232	100	319	100	586	100	195	100	166	100	225	100
Contacts given chemoprophylaxis	585	68	251	81	171	74	163	51	487	83	183	94	150	90	154	68
Penicillin	308	53	151	60	86	50	71	44	185	38	55	30	99	66	31	20
Sulfadiazine	56	10	33	13	15	9	8	5	77	16	57*	31	16	11	4	3
Erythromycin	10	2	5	2	4	2	1	1	4	1	3	2	1	1	..	..
Minocycline	49	8	15	6	15	9	19	12	128	26	55†	30	5	3	68‡	44
Rifampin	70	12	2	1	40	23	28	17	28	6	5	3	21	14	2	1
Ampicillin	22	4	9	4	2	1	11	7	43	9	6	3	4	3	33§	21
Tetracycline	21	4	8	3	9	5	4	2	2	<½	2	1	..	..	..	..
Penicillin and Sulfadiazine	19	3	19	8	..	..	..	..	..	..	..	..	..	..	..	..
Unknown	30	5	9	4	..	..	21	13	20	4	..	..	4	3	16	10

*Includes 35 hospital contacts to one case.
†Includes 51 school contacts to one case.
‡Includes 28 neighborhood contacts to one case and 30 co-worker contacts to another case.
§Includes 33 hospital and ambulance contacts to one case.
Source: State of California, Department of Health, Morbidity Records.

pared with 14 percent for meningococcal meningitis and 32 percent for meningococcemia with meningitis.

Serotype and Sulfa Sensitivity of Meningococcal Isolates

Of 385 cases reported during the years 1973 through 1975, a total of 75 meningococcal isolates were submitted for serotyping and sensitivity tests. Serotype B was the most frequent isolate in California. Only two out of 45 (4 percent) type B isolates were resistant to sulfa. Meningococcal organisms are defined as resistant if they continue to grow in the presence of a sulfa concentration greater than 10 μg per ml. Serotype C was isolated only 15 times, but 12 of the 15 (80 percent) were resistant. A total of 13 isolates were serotype Y and 1 (8 percent) was resistant; the remaining 2 were other serotypes. Data for the United States showed similar patterns of resistance for serotypes B, C and Y, but serotype B accounted for a smaller proportion of total isolates.

Meningococcal Disease Follow-up Report

The more detailed meningococcal disease follow-up report was completed for 235 of 351 (67 percent) civilian cases reported in 1973, 1974 and 1975. The demographic and disease characteristics of the group with detailed follow-up were similar to those for all cases reported in the three years.

Antibiotic Chemoprophylaxis

Of the 235 cases with detailed follow-up, 195 persons listed household contacts (Table 3). Chemoprophylaxis was administered to these contacts in 127 or 65 percent of households. A total of 862 contacts were listed on these case histories and 585 (68 percent) of them received antibiotic prophylaxis. In addition, 79 reports listed nonhousehold contacts. A total of 586 nonhousehold contacts were noted and 487 of them (83 percent) received antibiotics.

During the years 1973 through 1975, orally given penicillin was administered prophylactically to 53 percent of household contacts and 38 percent of nonhousehold contacts. The administration of penicillin and sulfa derivatives for prophylaxis of household contacts decreased from 1973 to 1975, while the administration of minocycline and rifampin increased during this period. Large numbers (28 to 51 persons) of nonhousehold contacts to five cases received chemopro-

phylaxis and inclusion of these persons tends to distort any temporal trends in chemoprophylaxis for nonhousehold contacts.

For the 585 household contacts who were treated prophylactically, treatment was begun in 223 (38 percent) within 24 hours of the time the initial patient was admitted to hospital; in 179 (31 percent), between one and two days after; in 51 (8.7 percent), between two and four days after; in 51 (8.7 percent), between four and seven days after, and in 17 (2.9 percent), antibiotics administration was begun a week or more after the initial patient was admitted to hospital. For 64 contacts (11 percent) the interval between admission of the initial patient and the start of prophylaxis was unknown.

Sulfa Sensitivity Testing and Antibiotic Use in Household Contacts

Sulfa sensitivity tests were reported on only 28 meningococcal isolates. Of these, 19 (68 percent) were sensitive to up to 10 μg per ml of sulfa and 9 (32 percent) were resistant. For 15 of the 19 cases with isolates sensitive to sulfa, household contacts were listed. In seven (47 percent) of the 15 households with contacts, sulfa was administered prophylactically. In eight households with contacts to a strain sensitive to sulfa, contacts were not given that drug. Contacts were noted in seven of the nine households in which the isolate was a resistant strain, yet contacts received sulfa in two of these seven households. There remained 173 households which listed contacts on the follow-up report but for which no sensitivity tests were done; despite this, the contacts in 11 (6.4 percent) of these 173 households received sulfa chemoprophylaxis when its value was unknown.

Nasopharyngeal Culture and Antibiotic Use in Household Contacts

Cultures were obtained from 198 of the 862 household contacts reported; 122 of these (62 percent) were given antibiotics while 76 (38 percent) were not. Of the 644 contacts for whom cultures were not obtained, 463 or 70 percent were treated prophylactically and 201 or 30 percent were not. Of 198 cultures obtained from contacts, 21 (11 percent) were positive for meningococci. Twenty of these 21 positive contacts received antibiotics. But 102 (58 percent) of the 177 contacts in whom cultures were negative were also treated with antibiotics and the remaining

TABLE 4.—*Associated Cases of Meningococcal Disease in California, 1973-1975*

FIRST CASE		*SECOND CASE*					
Age	*Isolate Serogroup*	*Age*	*Interval Since Admission to Hospital of First Case*	*Isolate Serogroup*	*Relationship or Nature of Contact with First Case*	*Chemoprophylaxis Before Onset*	*Remarks*
9 yrs	None	14 yrs	<1 day	None	Cousin	None	Both recovered, may be co-primary
12 yrs	None	9 yrs	<1 day	None	Sister	None	Both recovered, may be co-primary
9 mos	B	9 mos	9 days	None	Families of two patients are friends and neighbors	V-cillin K® 125 mg qid for 4 days, begun five days before onset of illness	First patient died, second recovered
17 yrs	B, sulfa resistant	39 yrs	6 days	B, sulfa resistant	Roommate to index patient	None	All secondary patients slept in home of index patient at least one night two to four days before onset of first case
		19 yrs	8 days	None,* cerebrospinal fluid smear positive	Friend, visited home of index patient one day	None	
		22 yrs	7 days	B, sulfa resistant	Visited home of index patient one day	None	
		18 yrs	17 days	B, sulfa resistant	Household contact of index patient	None	
1½ yrs	None	9 mos	3 days	None	Brother	None	Index patient died, both secondary patients recovered
		3 yrs	3 days	None	Brother	None	

*Received antibiotics for 2 days before hospital admission.

Source: State of California, Department of Health, Morbidity Records.

75 (42 percent) were not. Clearly the decision to treat prophylactically was not directly related to culture results; however, results probably influenced the decision to treat persons in whom cultures were positive.

Occurrence of Secondary or Associated Cases

During the years 1973 through 1975, five groups of associated meningococcal disease cases occurred in California (Table 4). The first pair of cases occurred in cousins who were admitted to hospital one day apart. Illness in the second pair, in sisters, began about the same time. The first and second pairs may be considered coprimary cases, as their onsets were less than 24 hours apart. The families of both pairs of patients were given penicillin prophylactically after admission of the second patients. The third pair of cases occurred in neighboring families. The follow-up report indicates that in the second case of the third pair, penicillin V potassium (v-Cillin K®) was prescribed (125 mg four times a day for four days) after admission of the first case, and two days after the patient completed this course of therapy, meningococcal disease developed.

The fourth group of cases involved meningococcal illness in a 17-year-old boy, followed by four other cases 6 to 17 days later. In all secondary cases the patients visited the home of the index patient and slept there for at least one night during a three day period immediately before admission to hospital of the index patient. Chemoprophylaxis with rifampin was instituted only after three secondary cases occurred. In the last secondary case the patient did not receive chemoprophylaxis.

In the fifth set, three cases occurred within three days in one household: meningococcal disease developed in two brothers three days after another sibling became ill.

Subtracting the initial cases in these five groups, we obtain a total of nine secondary or coprimary cases among 862 household contacts. Associated cases then occurred in 10.4/1,000 household contacts and in five of 195 or 2.6 percent of households where contacts were noted.

Discussion

At present, group A meningococci rarely cause disease in the United States; groups B, C and Y account for most reported cases.[1] Nor has the United States had any large outbreaks of meningococcal disease in recent years. In California the incidence of this disease has declined to its lowest recorded level. It is generally believed that use of group C meningococcal vaccine in military recruits since 1971 has been responsible for the pronounced reduction in disease incidence in that high-risk group. The reasons for the concomitant decrease in incidence among the civilian population are not known. Extensive epidemics of sulfa-resistant group A meningococcal disease have been observed more recently in many parts of the world, notably Brazil and Finland, and some epidemiologists have voiced concern about the possibility of outbreaks in this country should group A strains reappear.[2-4]

Outbreaks of group A meningococcal meningitis have been linked with high associated-case rates.[5] One of our objectives was to determine the associated-case rate for a period when group A meningococci were not prevalent. In our study, associated cases occurred at a rate of 10.4/1,000 household contacts or in 2.6 percent of households. Leedom and co-workers found an associated-case rate of 9.9/1,000 in contacts to 290 cases of meningococcal disease.[6] These rates are higher than the 4/1,000 rate reported by the Meningococcal Disease Surveillance Group who studied 326 cases that occurred in selected states between November 1973 and March 1974.[5] However, in all these studies the incidence of meningococcal disease in household contacts was several hundred times greater than the incidence in the general population. Virtually *all* of the associated cases in the studies cited occurred in *household* contacts: associated cases rarely, if ever, were observed in school or job contacts. In our study all associated cases developed in household contacts.

Clearly, it is necessary to prevent or rapidly recognize secondary cases among household contacts. However, our study showed that there is confusion and misunderstanding among physicians about the rationale and need for management of meningococcal case contacts, and about the appropriate drug regimens to use. Tests of household and other contacts for meningococcal carriage are of little value because chemoprophylaxis for close contacts should not be delayed until culture results are available. While it is not generally appreciated, there are good reasons for giving chemoprophylaxis to close contacts regardless of test results. A person in whom a culture is negative is probably at greater risk of disease should he or she acquire a pathogenic strain from a case or a carrier. Treatment of carriers is indi-

cated since carriage may represent recent acquisition of the organism and also because effective treatment halts spread of the organism. Despite the limited utility of culture findings, cultures were obtained in approximately a quarter of contacts in our study and often chemoprophylaxis was delayed or inappropriately not offered to those in whom results were negative.

Chemoprophylaxis is considered unnecessary for nonhousehold contacts such as schoolmates or co-workers. However, of the 586 nonhousehold contacts identified in our follow-up study, 487 or 83 percent received chemoprophylaxis. This figure may be exaggerated by a tendency to recall and list those nonhousehold contacts who were given antibiotics or who submitted specimens for tests. A review of the prophylactic regimes used by California physicians indicates a diversity of opinion about the appropriate or most effective agents to be used for prevention as well as a decided overuse of chemoprophylactic agents. The elimination of meningococci carried in the nasopharynx is considered necessary for any antibiotic or drug to be an effective prophylactic agent. Before the emergence of sulfa-resistant meningococci during the mid-1960's, sulfadiazine was a very effective prophylactic agent and was routinely recommended for all close contacts to cases. During 1974 about a quarter of all meningococcal isolates from cases and the vast majority of group C isolates were considered resistant to sulfa.[1] Our data show that contacts in two households improperly received sulfa as the initial drug. Sulfadiazine should not be used routinely unless it is known that the pathogenic meningococcal strain is sulfa sensitive. However, strain sensitivity usually is not known before prophylaxis must be initiated.

Orally given penicillin has been widely used as a prophylactic agent. In our follow-up study, it was the most frequently used agent from 1973 to 1975. However, penicillin is not considered to be the prophylactic agent of choice since it suppresses but does not eradicate meningococci from the nasopharynx.[7-9] Furthermore, meningococcal disease has been reported to occur in persons who were given penicillin prophylaxis.[10] In one of our associated cases, disease developed in the patient two days after a course of penicillin prophylaxis was completed.

More recently, rifampin and minocycline have been recommended for chemoprophylaxis but minocycline has fallen into disfavor because of the reported high incidence of side reactions.[11-13] The chemoprophylactic agent which is currently recommended by the Center for Disease Control is rifampin;[14] the recommended dosage is 600 mg twice a day for two days for adults, 10 mg per kg of body weight twice a day for two days for children aged 1 to 12 and 5 mg per kg of body weight for two days for infants aged 3 months to 1 year.[11] It has been found to be relatively effective in eliminating nasopharyngeal carriage and is considered to be the best available agent for chemoprophylaxis. Yet meningococcal disease has been reported in a contact who received rifampin.[15] Therefore, no chemoprophylactic agent can be considered completely effective and that probably contributes to the multiplicity of agents and schedules used in medical practice. In our opinion, close medical observation remains the most essential factor in the management of household or other intimate contacts to a case of meningococcal disease. Contacts should be instructed to consult their physician immediately upon development of fever. For contacts in whom fever develops within a week of onset in the index case, tests should be done promptly regardless of whether or not they received prophylaxis.

The United States Public Health Services' Advisory Committee on Immunization Practices has recently recommended use of the newly licensed meningococcal vaccines as an adjunct to chemoprophylaxis for household contacts.[14] We seriously question the utility of this recommendation since the potential benefit of vaccine administration is very low. Surveillance data indicate that almost three quarters of all cases that occurred in the United States during the past three years are due to meningococcal groups for which no vaccine is currently available. Given the short incubation period for this disease and the fact that protection cannot be expected until almost two weeks after vaccine administration, it is unlikely that a sufficient number of associated cases could be prevented to warrant routine vaccination of household contacts.

Case fatality rates in this study seem to be somewhat higher than the 6 percent to 11 percent reported for patients admitted to hospital with meningococcal disease.[16] A possible explanation is suggested by the finding that only 50 percent of patients admitted to hospital with meningococcal disease are reported (California Department of Health, Infectious Disease Section: Methodological studies of communicable disease reporting,

unpublished data), while all death certificates and laboratory reports which mention meningococcal disease are investigated routinely and added to the case file when indicated. In our surveillance system, meningococcal deaths are less likely to escape detection than are cases, and this probably accounts for the higher case fatality rates.

Many factors contribute to inaccuracy in incidence rates calculated from surveillance data; the most important are undoubtedly incomplete reporting of known cases and misdiagnosis. Misdiagnosis may occur in two ways: disease due to some other organism may be attributed to meningococci or meningococcal disease may be incorrectly thought to be due to some other organism. Of the four criteria for acceptance of cases in this study, two allow for inaccuracy: diagnosis by a physician without laboratory confirmation and meningococcal infection listed as the cause of death on death records. Cases with both clinical and laboratory evidence of disease or those counted on the basis of meningococci in blood or spinal fluid can be accepted as correctly classified. In order to minimize errors of classification, all reports of meningococcal disease without laboratory studies and all death certificates that mention meningococcal infection are routinely reviewed by medical epidemiologists. Case reports or death records with doubtful symptomatology or course of illness are queried and hospital or autopsy records are sometimes requested. Cases which raise serious doubts are not counted. These procedures limit the number of errors made by including cases incorrectly attributed to meningococci but still leave unassessed the number of cases of meningococcal disease incorrectly attributed to some other infectious agent when in fact the illness was caused by meningococci.

We know from our study, and from another which also found that 50 percent of patients admitted to hospital because of meningococcal meningitis were reported,[17] that we receive reports on only half of the diagnosed cases. Clearly our numerator data are limited for describing meningococcal disease incidence precisely. However, despite inaccuracies, the data are valuable for describing general trends since it is unlikely that reporting habits and misdiagnoses change radically over a short time. Further, inaccuracies in the numerator would not affect information about contacts and chemoprophylaxis.

In conclusion, our study findings indicate that many physicians are unaware of the following: (1) nonhousehold contacts are at little or no risk of contracting meningococcal disease; (2) prophylaxis should be offered *only* to household or intimate contacts immediately upon identification of an index case without waiting for test results for meningococcal carriage; (3) valid medical and epidemiological indications exist for administering prophylaxis to household contacts who are culture negative as well as those who are culture positive; (4) the current drug of choice for prophylaxis is rifampin, but since no drug is completely effective, close medical observation remains the most important factor in the management of household or intimate contacts to meningococcal disease.

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Refer to: Antoniskis A, Anderson BC, Van Volkinburg EJ, et al: Feasibility of outpatient self-administration of parenteral antibiotics. West J Med 128:203-206, Mar 1978

Feasibility of Outpatient Self-Administration of Parenteral Antibiotics

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It is customary to treat patients with infective endocarditis or osteomyelitis for a prolonged period in hospital with parenteral antibiotics. It was felt that it might be feasible to allow parenteral administration of antibiotics by the patients themselves at home. Results in 13 patients who administered antibiotics parenterally themselves (experimental group) were compared with those in 7 patients (control group) treated entirely within the hospital. Antibiotic-related complications were similar in both groups. There was no instance of infection of the intravenous cannula in either group. The average daily cost of antibiotic therapy decreased from $243.22 for inpatients to $69.35 for outpatients. The average cost of illness was $6,357.22 in the experimental group and $10,022.23 in the control group. If patients are carefully selected and well educated, the outpatient self-administration of antibiotics parenterally is both economical and safe.

ACUTE HEMATOGENOUS OSTEOMYELITIS and bacterial endocarditis are serious infectious diseases for which up to six weeks of therapy with parenterally administered antibiotics is recommended.[1-3] It is often difficult for patients or their physicians to accept the long hospital stays and the resulting high cost. In addition, many patients feel well after one to two weeks of therapy and become frustrated with a continuing requirement to remain in a hospital. It seemed feasible, therefore, to discharge these patients and have them continue their parenteral antimicrobic therapy at home with proper education and supervision. This report describes our experience using this procedure with 13 patients.

Methods

The clinical records of one of the authors (DNG), an infectious diseases consultant, were reviewed for the years 1971 through 1976. During this time, 20 patients received parenterally given antibiotics for several weeks for either acute osteomyelitis or bacterial endocarditis. Thirteen patients received a portion of their therapy as outpatients and were considered the experimental group; seven patients were treated entirely within the hospital and were considered the control group.

All 13 patients in the experimental group had a serious infectious disease process requiring parenterally given antibiotics, and the skill and intelligence to administer antibiotics at home. All agreed to comply with the specifications of outpatient administration and follow-up. All patients were in the hospital for initial diagnosis and treatment. Diagnoses in all patients were confirmed bacteriologically in the hospital's microbiology laboratory. No patient was considered a candidate for the outpatient use of parenteral antibiotics until the infectious process had responded clinically to treatment, and the patient was afebrile for at least five days. Then the patient and at least one family member were instructed by the hospital IV Department in (1) aseptic technique during antibiotic preparation and administration, (2) adverse reactions to the

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Submitted, revised, September 9, 1977.

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prescribed drug, (3) complications of the intravenous (IV) cannula and (4) the mechanics of IV antibiotic administration. Before discharge from the hospital the patients and participating family members were required to demonstrate their sterile technique in front of a member of the Infectious Diseases group. Patients were required to return to the IV Department every three days for insertion of a new IV cannula and to obtain fresh supplies. The patients were seen by their attending physician (DNG) at least once a week. Patients were instructed to return to the hospital emergency room if any immediate problems arose.

All intravenously given antibiotics were administered through a capped heparin-lock percutaneous forearm IV cannula. All patients were instructed to limit their activities during the treatment period to those that could be conducted within their residences.

Clinical and financial data were obtained from many sources, including hospital and physicians' medical records, records of the infectious diseases consultant (DNG), patient interviews and the hospital's business office records.

Results

Experimental Treatment Group

The bacteriologic and clinical diagnoses of the 13 patients are reviewed in Table 1. The group consisted of five females and eight males ranging in age from 12 to 61. In five patients the diagnosis was acute osteomyelitis, four cases due to Staphylococcus aureus and one due to Escherichia coli. In six patients the diagnosis was chronic osteomyelitis, five due to S. aureus and one due to Citrobacter species. The five chronic osteomyelitis patients were treated aggressively with a combination of surgical debridement and antibiotics for localized disease with sequestra. One patient was treated for S. aureus bacteremia and the last patient had Staphylococcus epidermidis endocarditis.

The outpatient antibiotic treatment regimens and complications are summarized in Table 2. As shown, a variety of antimicrobials were administered. In two patients, the development of hemorrhagic cystitis necessitated a change from methicillin to cephalothin. There was considerable variability in the duration of hospital treatment before beginning supervised outpatient drug use. However, the mean number of inpatient treatment days was 22. The duration of outpatient antibiotic administration ranged from 2 to 32 days with a mean of 21 days. Therefore, on the average, the duration of inpatient treatment and outpatient treatment was equivalent.

Four antibiotic-related complications occurred during the outpatient drug treatment (Table 2). In two patients methicillin hemorrhagic cystitis developed (reported in detail elsewhere).[4] In one patient treated with gentamicin, evidence of vestibular damage developed despite normal peak serum concentrations. One patient had complaint of diaphoresis and chills after each dose of penicillin G. It is of interest that two additional antibiotic-related complications occurred during treatment in hospital. In case 2 neutropenia developed, believed due to nafcillin. In case 8 a symptom complex of headache, myalgia, paresthesias and eosinophilia developed, attributed to cephalothin. Therefore, in the entire group there were two antibiotic adverse reactions during inpatient treatment and four adverse reactions during outpatient treatment.

All patients who suffered adverse drug reactions were successfully given alternative anti-

TABLE 1.—*Experimental Group: Diagnoses and Results of Therapy*

Case	*Age/Sex*	*Diagnosis*	*Duration of Followup and Outcome*
1. . .	51 F	Staphylococcus aureus acute osteomyelitis	No recurrence after 8 months
2. . .	15 M	S. aureus chronic osteomyelitis	No recurrence after 28 months
3. . .	28 M	S. aureus chronic osteomyelitis	Lost to follow-up
4. . .	45 F	S. aureus chronic osteomyelitis	Recurrence after 4 months
5. . .	23 F	S. aureus acute osteomyelitis	No recurrence after 9 months
6. . .	12 M	S. aureus bacteremia	No recurrence after 36 months
7. . .	46 F	Citrobacter species chronic osteomyelitis	Recurrence after 8 months
8. . .	21 M	S. aureus chronic osteomyelitis	No recurrence after 12 months
9. . .	47 M	Escherichia coli acute osteomyelitis	No recurrence after 10 months
10. . .	37 M	S. aureus chronic osteomyelitis	No recurrence after 18 months
11. . .	45 M	S. aureus acute osteomyelitis	Recurrence after 2 months
12. . .	52 M	S. aureus and several Gram-negative organisms, acute osteomyelitis	No recurrence after 17 months
13. . .	61 M	Staphylococcus epidermidis subacute bacterial endocarditis	No recurrence after 13 months

biotics without incident. None of the four patients in whom adverse drug reactions developed during outpatient treatment required readmission to the hospital.

For reasons other than adverse reactions, three patients did require readmission to complete their prescribed course of outpatient drug administration. Two patients had increasingly more frequent IV cannula changes because of venous thrombi and a resulting lack of superficial veins. The third patient, a 15-year-old boy, was readmitted after only two days because his mother found it difficult to cope emotionally with the responsibility of outpatient antibiotic administration. The remaining ten patients had no major difficulties in preparing and administering antibiotics at home. Despite the recommendation that cannulas be replaced every three days, cannula replacement varied from once a day to every five days. Despite this variability, there no cannula site infections.[5-7] None of the patients complained about having to return frequently for cannula replacement; they accepted this inconvenience in order to remain outside the hospital.

Control Treatment Group

The bacteriologic and clinical diagnoses of the seven control patients are reviewed in Table 3. The group consisted of four males and three females with ages ranging from 12 to 72. All patients had osteomyelitis, four due to S. aureus, two due to Pseudomonas aeruginosa and one due to Serratia marcescens.

For a variety of reasons, none of these patients was a candidate for parenteral antibiotic therapy at home. Two patients had impaired mental faculties, four patients were severely immobilized by their other orthopedic therapy (for example, bilateral long leg casts in traction) and one patient could not speak English. Furthermore, three of the seven patients were receiving Medicare medical benefits in the hospital, but Medicare denied reimbursement for the same drugs self-administered as outpatients.

Three patients received a combination of gentamicin and carbenicillin therapy. Two patients were given methicillin, and cephalothin was prescribed for one patient. In one patient receiving cephalothin a skin exanthem developed, in a second patient receiving cephalothin there was a profound neutropenia, and in a third patient methicillin hemorrhagic cystitis developed.[4]

Cost of Parenteral Antibiotics

Cost factors for the inpatient and outpatient use of antibiotics were identified. For patients

TABLE 2.—*Outpatient Antibiotic Treatment: Duration and Complications*

Case	Antibiotic Dose/Day, Route	Days of Treatment: Inpatient	Days of Treatment: Outpatient	Complications
1. . .	Methicillin, 12 grams IV; then cephalothin, 12 grams IV	28	19	Hemorrhagic cystitis
2. . .	Nafcillin, 12 grams IV	41	2	None
3. . .	Penicillin G, 12 mil U IV	15	6	None
4. . .	Cefazolin, 6 grams IV	15	8	None
5. . .	Methicillin, 12 grams IV; then cephalothin, 12 grams IV	14	32	Hemorrhagic cystitis
6. . .	Vancomycin, 2 grams IV	25	11	None
7. . .	Gentamicin, 180 mg IM	9	30	Vestibular damage
8. . .	Cephalothin, 12 grams IV	16	16	None
9. . .	Cephalothin, 12 grams IV	27	21	None
10. . .	Penicillin G, 1.2 mil U IV	21	28	Post-infusion chills, diaphoresis
11. . .	Methicillin, 18 grams IV	11	29	None
12. . .	Ampicillin, 12 grams IV	39	6	None
13. . .	Cephalothin, 12 grams IV	21	21	None

IM = intramuscular IV = intravenous

TABLE 3.—*Control Group: Diagnoses and Results of Therapy*

Case	Age/Sex	Diagnosis	Results of Therapy
1.	72 M	Pseudomonas aeruginosa osteomyelitis	No recurrence after 48 months
2.	67 M	Serratia marcescens osteomyelitis	Recurrence after 10 months
3.	38 F	Staphylococcus aureus osteomyelitis	No recurrence after 36 months
4.	43 M	S. aureus osteomyelitis	No recurrence after 26 months
5.	74 F	S. aureus osteomyelitis	No recurrence after 18 months
6.	12 M	P. aeruginosa osteomyelitis	No recurrence after 12 months
7.	63 F	S. aureus osteomyelitis	No recurrence after 24 months

TABLE 4. *Results of Cost Analysis in Experimental and Control Patients*

	Experimental Group		*Control Group*
	Inpatient	*Outpatient*	*All Inpatient*
Average cost per day	$234.22	$69.35	$229.70
Average cost of illness	$6,357.52		$10,022.23

in hospital, daily costs were accrued for the hospital room, the antibiotic, IV tubing, dextrose solution, heparin flushes, the nurse administration fee and a daily physician's fee. For outpatients, daily cost factors included the cost of the drug, heparin flushes and other supplies for IV drug use. A weekly physician fee was used in calculation of outpatient costs. All costs were calculated on the basis of 1977 prices.

The results of the cost analysis are shown in Table 4. The average inpatient cost per day was similar for both the experimental and control groups. As anticipated, there was a dramatic reduction from $234.22 to $69.35 in the average daily cost when the drugs were given out of the hospital. For inpatients, the components of the total daily cost were as follows: room charge, 50 percent; antibiotic cost, 19 percent; dextrose solution and heparin flush costs, 24 percent; physician fee, 5 percent, and IV nurse administration fee 2 percent. Therefore, the major savings were in room costs, and to a much lesser degree in physician's fees. Comparing the average cost of illness for the two groups, an average saving of $3,700 per patient was achieved.

Discussion

The results of our experience support the feasibility of allowing patients to self-administer parenteral antibiotics with family assistance, thereby achieving easily measurable savings in expenses. Our major concern was, and continues to be, the potential hazards of such a program.[5-7] Our experience suggests that outpatient parenteral antibiotic self-administration is no more dangerous, and no less efficacious, than inpatient nurse-administered parenteral antibiotics—provided patient selection and education are appropriate. Six adverse antibiotic reactions occurred in the 13 patients of the experimental group. Two complications occurred during inpatient antibiotic administration and four occurred during outpatient antibiotic administration. There is nothing to suggest that treatment in hospital would have prevented the four outpatient antibiotic complications.

Several other points deserve emphasis. No patients required readmission because of drug toxicity. An occasional patient was unable to complete outpatient therapy because of paucity of veins or emotional problems with needles. However, there were no instances of a technical inability to mix the drug, connect tubing or insert needle into heparin lock. There were no instances of air emboli. There were no life-threatening antibiotic reactions. We believe our success is due largely to the extensive education program each patient received before leaving the hospital.

All patients were instructed to return to the hospital promptly if any problem, regardless of its seriousness, occurred. It is essential that good communication be maintained among the patient, the physician and all involved hospital departments. In our hospital letters of instruction explaining the patient's special status were sent to the hospital pharmacy, IV Department, and Emergency Department at the time of discharge.

Assuming that prolonged parenteral therapy does result in fewer relapses and is therefore desirable, it is likely that many patients are denied prolonged treatment because of either the expense or the confining nature of prolonged hospital stays. Therefore, outpatient parenteral antibiotic self-administration allows patients to have a more normal life, saves money, appears to be safe and may contribute to a better clinical result.

Unfortunately, the regulations of many health insurance carriers provide only partial or no reimbursement for the cost of outpatient medication. Several smaller insurance companies have honored such claims after the inherent dollar savings were explained. Despite extensive documentation of dollar savings, to date both Medicare and Blue Cross have not altered their regulations regarding this special use of outpatient drugs.

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Refer to: Shore JH: The commitment process for psychiatric patients—Changing status in the western states (Medical Progress). West J Med 128:207-211, Mar 1978

The Commitment Process for Psychiatric Patients

Changing Status in the Western States

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Recent changes in commitment legislation for the mentally ill have had an important impact on the role of physicians in treating these patients. New commitment laws emphasize civil rights at the expense of right-to-treatment concepts, sometimes causing neglect of severely psychotic persons. Only four western states have a high rating of conformity with a model commitment statute.

IN THE PAST DECADE there has been great progress in expanding the treatment resources and defining civil rights for patients who are involved in the civil commitment process. Many western states have adopted new civil statutes[1-3] which emphasize patients' civil liberties under the commitment process, alternatives to hospital commitment and community-based treatment resources. Since 1969 Oregon, Washington and California have all adopted new commitment statutes. This paper will review these recent changes in commitment legislation and discuss their impact on the physician's role in the treatment of patients with mental illness.

The recent interest in providing due process for all citizens has received particular emphasis for the mentally ill. Society's attitudes in decisions by the courts have contributed to the atmosphere in which new commitment legislation has been developed. In 1972 the American Psychiatric Association published a position statement[4] on involuntary admission to hospital of the mentally ill. The statement contained four major points:

- Most persons who need hospital care for mental illness can be and should be informally and voluntarily admitted.
- Psychiatrists should use community-based outpatient facilities, avoiding hospital admission whenever possible.
- Involuntary treatment is necessary for the few patients who will endanger themselves or others because of a mental illness, and who are unable to make a free and informed decision.
- Persons involuntarily admitted to hospital must be provided full rights of due process and judicial review.

In redefining the right to treatment with legal justification from the United States Constitution, federal judges recently have written several landmark decisions that have affected the commitment process. *Wyatt vs Stickney* was a suit that

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dealt with conditions in the hospitals run by the Alabama Department of Mental Health. The court ruled against the State by declaring:

> To deprive any citizen of his or her liberty upon the altruistic theory that the confinement is for humane and therapeutic reasons and then fail to provide adequate treatment violates the very fundamentals of due process.

In writing this standard the court sought to do more than prevent destructive conditions; it sought to insure adequate treatment. The trial judge detailed minimum medical and constitutional requirements to be met with dispatch. His decree set standards guaranteeing to patients basic rights to privacy, presumption of competency to handle affairs, communication with outsiders and so forth. Requirements were established governing staff to patient ratios, floor space, education, sanitation and nutrition. The court also ordered that individual treatment plans be developed, that written medication and restraint orders be filed, and that these be periodically reviewed.[5]

California, Oregon and Washington Laws

Legislatures in all three West Coast states responded to the current reform pressure and developed new mental health acts to define the commitment process for psychiatric patients. The California commitment bill, the Lanterman-Petris-Short Act, became effective in 1969. This legislation, one of the first commitment reform acts in the country, was hailed as a model in defining patients' civil liberties and emphasizing alternative to hospital treatment. New commitment laws for both Oregon and Washington followed and incorporated many of the basic reforms that had been dealt with in the California legislation. In Oregon the definition of a mentally ill person is formulated after statutes in the California commitment law and is stated in two parts:

> A mentally ill person means a person who, because of a mental disorder, is either—
>
> a. dangerous to himself or others; or
>
> b. unable to provide for his basic personal needs and is not receiving such care as is necessary for his health and safety.

Oregon, Washington and California all use the criterion of "dangerous" in the definition of a mentally ill person. In Washington the descriptive phrase reads "presents a likeliness of serious harm to himself or others." Oregon and California statutes read "dangerous to himself or others." Many legal experts have argued that the "dangerous" clause should be excluded because in criminal law a person cannot be incarcerated if he only contemplates crime and since the potentiality of dangerousness is sufficiently vague to allow commitment with few facts indicating mental illness. However, most commitment statutes do include a "dangerous" clause. The strictness with which the commitment court applies a legal definition to "dangerous" often determines the incompatibility that develops between legal and medical perspectives. This incompatibility is compounded by the inability of mental health professionals to accurately predict dangerousness.

The second clause expresses concern for chronic mentally ill patients and elderly persons with mental illness who are not capable of providing for their basic needs. Washington law defines this "greatly disabled" clause as a "condition in which a person as a result of mental disorder is in danger of serious physical harm resulting from failure to provide for his essential human needs." The California law has an alternative to involuntary commitment by providing for a conservatorship. Conservatorships are recommended for patients who are gravely disabled as a result of mental illness and are unable to provide for such basic necessities as food, clothing and shelter.

An important feature of Oregon's law is a mechanism for precommitment investigation by the mental health program director in each county. In Oregon, commitment takes place through the Mental Health Division rather than to one of the three state hospitals as in earlier commitment practices. The precommitment investigation is designed as a mechanism to encourage alternatives to commitment or to provide community treatment of the committed person if an alternative to admission to a state hospital can be planned. This precommitment investigation and postcommitment planning theoretically allows for greater flexibility in developing a community-based treatment alternative.

The patient's rights both before and after treatment are clearly delineated. These include the right to legal counsel and cross-examination of witnesses and examiners at the commitment hearing. If a person is committed, that person does not forfeit civil rights, such as voting or the right to make contracts. A committed person also has access to uncensored personal communication by phone or mail and the right to refuse unusual treatment, usually defined as electroconvulsive therapy or lobotomy. In the three West Coast states the commitment legislation defines a limited period of commitment which ranges from 90

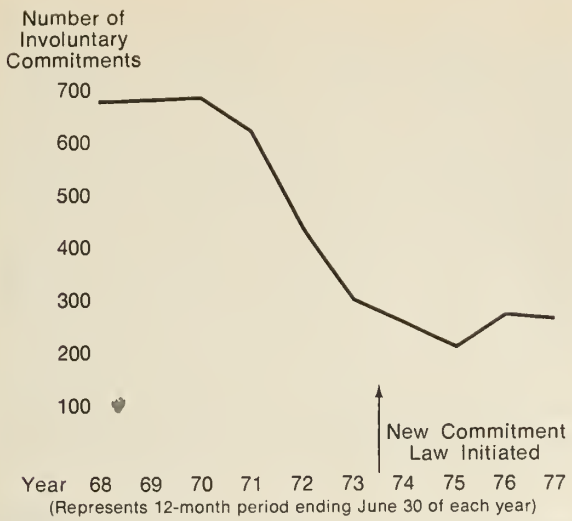

Figure 1.—Involuntary commitments in Oregon's largest metropolitan county, 1967-1977.

days in both Washington and California to 180 days in Oregon. Both Washington and California include a 14-day initial treatment period that precedes a longer commitment. This alternative has not been available in the Oregon law. Additional commitment for another period of 90 or 180 days can take place after proper review. In Oregon the precommitment investigators are always nonphysician mental health professionals who have not treated the patient. Their recommendations sometimes reflect a lack of appreciation of the seriousness of the illness if compared with the physician's perspective. On the other hand, physicians may overprescribe commitment in an effort to insure treatment in a desperate, but not "dangerous," mental health crisis. For instance, an uncontrolled manic patient may be destroying a marriage, a family and financial security but may not be dangerous in an immediate, life-threatening sense. With the new commitment laws this type of patient is now "free" to reject treatment, in spite of the fact that the rejection of help is a symptom of major mental illness.

Dramatic Changes in Commitment Rates

There have been downward trends in annual commitment rates for the state of Oregon and its largest metropolitan county since 1972. Although this preceded the implementation of Oregon's new commitment law, it coincided with a legal decision *(Coleman vs Oregon)* which affirmed that the alleged mentally ill person had to be represented by a lawyer unless he waived this right. In Oregon this ruling, preceding implementation of the new commitment law, appeared to be the most significant event related to changing commitment rates (Figure 1). The effect of lawyers who have become actively involved in decision making in involuntary hospital admission in other states has been documented. In New York City[6] a dramatic increase in discharge rates among those patients who requested a court hearing was noted. There is a positive association among (1) the presence of a lawyer, (2) duration of a hearing and (3) the likelihood of not commiting the patient to hospital.[7] Interpretation of such findings by participating psychiatrists suggests that the psychiatrists unwittingly negotiate an uneasy truce with lawyers and trade off effective authority to them.

The reported impact of new commitment statutes in providing effective mental health service has been dramatically different between West Coast states, and sometimes within each state. An evaluation of the California commitment law at the Sacramento Medical Center[8] showed that the median length of involuntary hospital stays was short (three to five days) and that 79 percent of patients had either agreed to voluntary hospital admission or had been discharged by the end of five days. A majority of patients (68 percent) accepted a recommendation for voluntary treatment although the research did not distinguish between committed and noncommitted patient groups for this "voluntary" follow-up. A lengthy involuntary treatment was rarely needed. In Oregon's largest metropolitan area 70 percent of all patients entering the commitment process also are released after a short involuntary evaluation and emergency treatment. However, only 44 percent of patients who receive the short, precommitment evaluation and treatment and who are not committed, make contact with recommended follow-up resources.[9]

A commitment system that turns acute mentally ill persons back on the street without follow-up should be defined as unsuccessful. Perhaps the technicalities of the law are correct; but a correct law can be poor medicine. Two factors may be significant in Oregon's lack of success in implementation of commitment law compared with California and Washington. First, Oregon's law does not include the 14-day treatment period that apparently has been successfully implemented in both California and Washington. (This provision was proposed as an amendment by Oregon's 1977

legislature.) In California the 14-day period of intensive treatment may be requested before the formal court review, unless rejected by the patient, and may avoid commitment and a longer hospital stay. In Sacramento a formal link between the evaluating hospital inpatient services and the community follow-up clinics is a vital component which influences the high percentage of effective outpatient referrals. This link is missing in Oregon's major metropolitan area where emergency, inpatient and outpatient services usually take place in separate treatment systems.

A Model Commitment Statute

Trefferte and Krajeck[10] have proposed a model state commitment statute and compared existing statutes of 47 states to this idealized model. They propose 15 major elements which are essential in a model statute. These include: (1) a clear statement of the legislative intent; (2) clear definitions to distinguish such terms as mental illness, dangerousness, gravely disabled, developmental disability, alcoholic patient and drug dependent patient; (3) encouragement of voluntary admissions; (4) admission of minors regulated by special procedure; (5) provisions for emergency commitment; (6) petition for involuntary commitment; (7) probable cause hearing must be held; (8) observation and judicial review before filing commitment (not to exceed 14 days); (9) dangerousness: the criteria for commitment; (10) patient's right to adequate treatment; (11) delineation of treater's rights; (12) determination of incompetency by separate proceeding; (13) emphasis on least restrictive alternatives to care; (14) commitment not indeterminant, and (15) recognition of spiritual therapy.

Among the western states, Washington, Arizona, Colorado and California have greatest conformity to provisions of this model commitment statute. Oregon, New Mexico, Nevada, and Wyoming have moderate conformity, while the remaining western states conform poorly to the model statute.

Conclusions

After developing the new approach to mental health in the California legislation, Petris[11] concluded that it is unrealistic to expect to accomplish both the legal and the medical objectives within the commitment system:

> The commitment court can be seen in two ways. Viewed the first way, it provides a legal process for removal of dangerous persons from the community to confined treatment facilities. If danger to the community is the issue and custody of the dangerous person is the objective, then medical considerations are secondary. Danger must be substantiated by the legal process and confinement is required to protect the community and treat the offender. The commitment courts and the state hospitals are now expected to perform these protective and treatment functions.
>
> Viewed the second way, the commitment courts provide a means of securing professional help for mentally disordered persons who will not accept treatment. If finding mental illness is the issue and providing prompt treatment the objective, then legal considerations are secondary. Accurate medical, psychological, and social evaluations are required to substantiate the nature of the problem, and an appropriate treatment program is required. The commitment courts and the state hospitals are also expected to perform these functions.

Appeal court rulings often reinforce legal technicalities and widen the gap between legal and medical perspectives. In Oregon an appeal court recently has declared *(State vs O'Neill)* that a precommitment psychiatric hospital record cannot be reviewed in the commitment hearing because of the patient's confidentiality privilege. And yet in this courtroom setting, mental health examiners are required to give an informed opinion concerning a patient's mental illness and commitment. The patient's symptoms must be compatible with precise definitions of behavior within the new commitment statutes. This applies to a significantly smaller group of patients than the older commitment laws. However, we cannot assume that a more enlightened legal approach to the commitment of psychiatric patients is necessarily related to more humane or effective treatment since the implementation of these laws in some states has definitely blocked access to treatment for a group of severely disturbed psychotic persons. In a recent review of mental health litigation, Stone[12] has outlined the difficulty of our tasks:

> The kinds of patients for whom involuntary confinement may be deemed appropriate are typically panicked and terrified. They are wary and distrustful or agitated and difficult to reach. Their families and friends are often exhausted and desperate after having been caught up in the patient's pathology and their own responses to it. The complicated human dynamic of crisis is what the psychiatrist (physician) must confront.

The recent advances in new commitment legislation for the mentally ill have emphasized a protection of rights and nonhospital care. The commitment process is no longer available as a means of providing treatment for many uncooperative, psychotic patients. This has created new problems for patients who were formerly

commitable, and who now may receive no effective follow-up service or who are charged with minor criminal offenses.[13] These problems may be particularly acute in some western states where the evolution of new commitment practices is not associated with advances in the nonhospital, ambulatory mental health delivery system. In addition, commitment legislation often excludes particular safeguards that would eliminate some of these barriers to treatment. For example, few states include a definition of the treater's rights (15 percent) or optional 14-day treatment before full judicial inquiry (13 percent).[10] These particular components of commitment statutes insure attention to issues of adequate treatment which complement the emphasis on civil rights.

The physician's role as patient advocate is brought into sharp focus by these changes in the commitment process. A significant group of ambulatory psychotic patients, formerly treated within the commitment process, are now excluded from any treatment system, either involuntary or voluntary. In addition, many of our commitment statutes require amendment to realistically deal with the patients' right to adequate treatment.

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—WILLIAM R. OLSEN, MD, *Ann Arbor*

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Refer to: Merritt TA, Gluck L, Higgins C, et al: Management of premature infants with patent ductus arteriosus (Specialty Conference). West J Med 128:212-222, Mar 1978

Management of Premature Infants With Patent Ductus Arteriosus

WILLIAM L. NYHAN, MD, PH D:* *Tiny premature infants, already compromised by the respiratory distress syndrome, frequently have the additional problem of a patent ductus arteriosus. We shall consider the recognition of patent ductus arteriosus within the context of seriously ill premature infants and the correlation of radiologic and clinical findings, and examine the experience at the University of California, San Diego* (UCSD), *with this problem. This will lead to a review of the exciting new developments in the field of prostaglandin pharmacology and their relevance to clinical management. We shall start with a consideration of the clinical problem by Dr. Gluck.*

LOUIS GLUCK, MD:† Discussion of the ductus begins not with the cardiologist but with the physician who looks after the newborn infant. It is our firm belief after a significant experience with patent ductus arteriosus that we, not cardiologists, are the ones who should make the diagnosis first. I shall try to amplify and clarify this statement.

Historically the ductus first was mentioned in the writings of Galen in the second century AD. He dissected and described the first ductus arteriosus. It was subsequently described approximately 15 centuries later in Italy by Leonardo Botallo. The first medical concern with the ductus came in about 1900, when Gibson described the classic machinery murmur and discussed the ductus as a clinical entity. Then seven years later, in 1907, Munro described the first surgical approach, but it was not until 1938 that Gross for the first time successfully closed the ductus.

There has been an understanding of the complications of patent ductus arteriosus (PDA) in premature infants—although we like to think that this is very recent—since the mid-1950's. We may perhaps get the mistaken notion that it was not until the advent of continuous positive airway pressure (CPAP) that we began to appreciate the patent ductus in small babies. However, Eric Burnard, while a Visiting Fellow at Columbia University and Babies Hospital in the mid-1950's, described patent ductus arteriosus as a complication of hyaline membrane disease. This led, in fact, to another misconception, held for a long time, that patent ductus arteriosus and consequent heart failure were "what hyaline membrane dis-

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ABBREVIATIONS USED IN TEXT

CPAP = continuous positive airway pressure
FIO_2 = forced inspiratory oxygen
LA/AO = left atrial to aortic (ratio)
PDA = patent ductus arteriosus
RDS = respiratory distress syndrome
UCSD = University of California, San Diego

ease was all about." What Burnard found was that in every baby with hyaline membrane disease a definite murmur developed at some time or other. He chose to believe that respiratory distress syndrome (RDS) or hyaline membrane disease was really a complication of cardiac disease, and the theory was proposed that hyaline membrane disease represented a unique form of chronic congestive heart failure.

Although the cause of the disease is not congestive failure, it is true that by the time a premature infant has lived long enough and has begun to get better, he usually will show this complication. One might state that in very small babies the incidence of patent ductus, whether significant or insignificant, must be considered 100 percent.

Although it had been known for many years that patent ductus was a major complication in very small babies, it usually was diagnosed terminally, and these infants went on to death. A major contribution of CPAP has been to keep these small babies alive. Whether or not they ultimately survived, they were now living long enough for the patent ductus to be recognized as a definite clinical entity and as an important early complication of hyaline membrane disease. In San Francisco, here at UCSD and in a few other places where CPAP techniques were in wide use, everyone began to have the same experience. The babies with RDS would continue to get better up to a point, and then they would get worse. As we improved our techniques for managing babies with RDS the early diagnosis of PDA became much more subtle. We now have a unique situation where I think the kind of mechanical support of ventilation that we give a small premature infant with RDS leaves little residual problem in the baby's lungs. As a consequence, the diagnosis of patent ductus becomes possible even on the first day of life. The hemodynamics in premature infants are somewhat different than in larger newborns. They do not have comparable pulmonary arteriolar musculature. Systemic pressure is much lower, and in many instances we see the development of pulmonary edema very early.

In current and proper management of a baby with hyaline membrane disease, the usual story is that the baby progresses to some degree of ventilatory failure. The baby is treated with mechanical ventilation, because we feel this is the least harmful way to treat ventilatory failure. The baby then begins to improve. First the fractional inspired oxygen (FIO_2) can be lowered. Whereas treatment may have been started at somewhere over 60 percent FIO_2, perhaps 80 or 90 percent, very promptly this can come down to perhaps 50 percent. The arterial oxygen pressure (Pa_{O_2}) remains high, the baby oxygenates well and continues to improve, and ventilatory assistance can be reduced more and more. In a weaning schedule, we are ready to take the baby off the ventilator, and then we arrive at a point at which the baby does not get any better. At this time we may or may not hear a murmur of PDA, and we may or may not see changes on x-ray studies, and the pulses may or may not be bounding. The liver may or may not get larger, and the heart may or may not get bigger, but we are faced with a situation in which the baby has stopped getting better.

When PDA is not a complication, the baby does get better. We use a weaning schedule and finally take the baby off the ventilator. Usually they do very well.

In a baby in whom the PDA is a significant complication, the classic story is for the baby just to stop getting better. Pulmonary edema does, indeed, develop. Carbon dioxide begins to accumulate. More ventilation is required and a little more oxygen will be required. At this point, generally the baby does have some cardiomegaly. The liver may be down a bit, and on x-ray studies shunt vessels begin to be seen, along with evidence of pulmonary edema.

I have emphasized the earliest findings in babies with PDA and the fact that these findings are subtle. They do not present as sudden overwhelming cardiac disease, as we have considered the ductus in years gone by. This is approached at first as a statistical variation in the way the babies should be progressing. They simply stop getting better in spite of excellent management.

In this situation the commonest complication to be considered is patent ductus arteriosus.

DR. NYHAN: *In view of the subtle early manifestations of this complication so clearly presented by Dr. Gluck it would be of interest to develop objective measures to evaluate these babies' condition. Dr. Charles Higgins has been concerned with roentgenographic approaches to the determination of when difficulties are beginning in infants, and he will discuss these aspects of the problem now.*

CHARLES HIGGINS, MD:* In spite of the frequency of the problem of PDA in preterm infants with RDS, surprisingly few data are available that correlate the sequential radiographic findings with the clinical course or the echocardiographic findings. In order to obtain this type of correlation, we recently evaluated sequential radiographic findings in a group of 55 infants with PDA in the setting of RDS, along with the clinical and echocardiographic findings.[1] The sequential radiographic findings we assessed were increases in pulmonary vascularity and cardiomegaly. Clinical severity was the measure of the left-to-right shunt. The echocardiographic marker of a large shunt was an abnormal left atrial-to-aortic ratio. In order to confirm that the radiographic findings were, in fact, due to the PDA we noted regressive changes in the pulmonary vascularity and cardiomegaly after closure of the shunt.

TABLE 1.—*Criteria for the Assignment of Infants to Each of the Study Groups, and Numbers of Infants in Each Group*

CLINICAL GRADES

1. *Small shunt* (7 infants)
   Intermittent murmur
   Normal pulses
2. *Moderate shunt* (11 infants)
   Systolic murmur
   Prominent pulses
   Infrequent episodes of apnea/bradycardia
3. *Large shunt* (37 infants)
   Systolic/diastolic murmur
   Bounding pulses
   Multiple episodes of apnea/bradycardia
   Respirator dependency
   Hepatomegaly

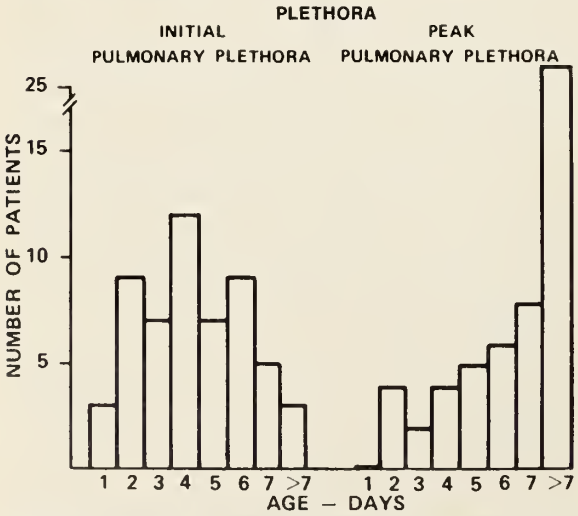


Figure 1.—Ages of onset and peak of increase in pulmonary vascularity.

*Associate Professor of Radiology.

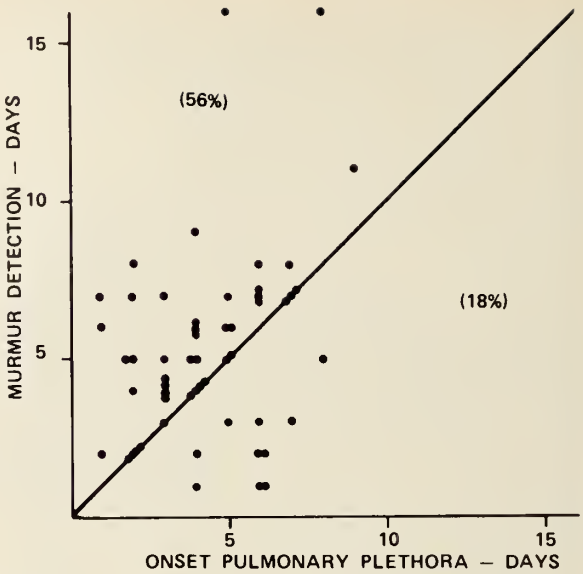


Figure 2.—Correlation of the detection of a murmur with roentgenographic evidence of increase in pulmonary vascularity.

The 55 infants with PDA were divided into three groups, on the basis of the clinical severity of the shunt. The number of patients in each group and the criteria for inclusion in each category are indicated in Table 1. Most of the patients fell into the large shunt category. This may reflect the fact that there is a greater likelihood that in a child with a large shunt there will be sequential radiographic examinations.

Figure 1 provides data on plethora and the age at which peak pulmonary vascularity was observed. The time of onset was usually between the second and sixth day. Most patients present with increase in pulmonary vascularity within the first week of life. However, the time of peak

increase in pulmonary vascularity is usually delayed until the end of the first week or during the second week. Figure 2 relates the time that a murmur was detected clinically with the radiographic appearance of increase in pulmonary vascularity. In 56 percent of the infants there was radiographic evidence of increase in pulmonary vascularity before murmur detection; that is, at least 24 hours before the clinical detection of a cardiac murmur. In 26 percent of patients there was simultaneous appearance of the murmur and increase in pulmonary vascularity. The clinical detection of a murmur occurred before the radiographic observation of pulmonary plethora in only 18 percent of these infants.

There was no significant difference in the time of onset or time of peak pulmonary vascularity between those patients with small or moderate-volume shunts and those with large-volume shunts. Pulmonary edema was seen almost exclusively in patients with large-volume shunts. This was true for perihilar edema as well as generalized pulmonary edema. In only a single patient with a moderate-volume shunt was there radiographically apparent pulmonary edema.

A typical radiographic sequence in a child with a large-volume shunt is portrayed in Figure 3. The radiograph on the first day of life showed a normal cardiac size, evidence of some hyaline membrane disease and some retained lung fluid. The radiograph on the fourth day of life showed substantial pulmonary plethora, perihilar pulmonary edema, and an increase in cardiac size. This is the radiographic sequence which is observed when hemodynamically significant ductal left-to-right shunting has ensued in a patient with RDS.

In order to derive numbers with which to quantitate the signs of a large-volume shunt, we compared the peak cardiothoracic ratio in the patients in each of the three groups. In infants, cardiomegaly is usually not considered to be present until the transverse cardiothoracic ratio is over 60 percent. There was only one patient with a moderate-volume shunt in whom the cardiothoracic ratio was greater than 60 percent. However, only a third of patients with large-volume shunts had cardiomegaly. Therefore, while this sign is relatively specific for a large-volume shunt, it is extremely insensitive. Moreover, there was considerable overlap in the values of the peak cardiothoracic ratio in the large-volume group when compared with the groups of smaller-sized shunts.

The increase or change in cardiothoracic ratio was compared among the three groups of infants. The change in cardiothoracic ratio was calculated as the increase in this ratio between the radiograph on the first day of life, and the maximum cardiothoracic ratio. An increase in ratios of 0.05

Figure 3.—Progression of evidence of left-to-right shunt in an infant with a patent ductus arteriosus.

or greater was considered to be indicative of a large-volume shunt. In 78 percent of patients with large-volume shunts there was a cardiothoracic ratio that increased 0.05 or more. This represents at least a 10-percent increase in cardiac size. On the other hand, in only a small number of patients with moderate-volume shunts was there a significant increase in cardiothoracic ratio.

The other modality for the objective evaluation of the severity of the left-to-right shunt is the echocardiographic determination of the left atrial-to-aortic (LA/AO) ratio. Patients with large-volume shunts usually have a LA/AO ratio of greater than 1.0.[2] In most of the patients in this group, actually in all but nine patients, there were LA/AO ratios greater than 1.0. However, in nine patients with a large-volume shunt, LA/AO ratios were less than 1.0. In other words, by echocardiographic measures, these patients would not have been considered to have large-volume shunts. In eight of these nine patients there was increase in the cardiothoracic ratio as determined by sequential thoracic radiographs. Therefore, in all but one patient with a large-volume ductal shunt, the condition would have been detected by using a combination of radiographic evaluation and sequential echocardiographic evaluation.

Figure 4 illustrates the close correlation of radiographic findings with echocardiograms in a child with a large-volume left-to-right shunt. A radiograph on the eighth day of life showed pulmonary edema and large segmental pulmonary arteries with perihilar pulmonary edema, alveolar pulmonary edema in the lower lobes and a cardiothoracic ratio which had increased greater than 0.05. An echocardiogram obtained on the same day showed that the LA/AO ratio was notably elevated. The LA/AO ratio, which was measured during systole as the ratio of the dimension of the aorta and the dimension of the left atrium, was greater than 1.4. There was clear evidence, therefore, of a large-volume left-to-right shunt.

In the group of 26 patients in whom surgical operation was carried out, radiographs were evaluated on each of the postoperative days for a week following operation. After operation, the cardiothoracic ratio dropped almost immediately to within the normal range. The average decline in the ratio on the first postoperative day was 0.07 which was greater than a 12 percent decrease. By the seventh day after operation, the cardiothoracic ratio was identical to that on the first day of life.

Figure 5 illustrates this process in a sequence of chest x-ray studies. On the first day of life, there was evidence of granularity throughout the lungs, indicating hyaline membrane disease, and a normal-sized heart. By day 11 there was perihilar pulmonary edema and a significant increase in cardiothoracic ratio. On the fourth postoperative day pulmonary vascularity still remained somewhat abnormal, but there had been a substantial decrease in the cardiothoracic ratio.

In conclusion, pulmonary plethora may be detected by radiographic evaluation before detection of a murmur. Cardiomegaly is a relatively insensitive sign of a large-volume shunt, which was present in only a third of patients with large-volume left-to-right shunts. However, sequential radiographic and echocardiographic evaluation is

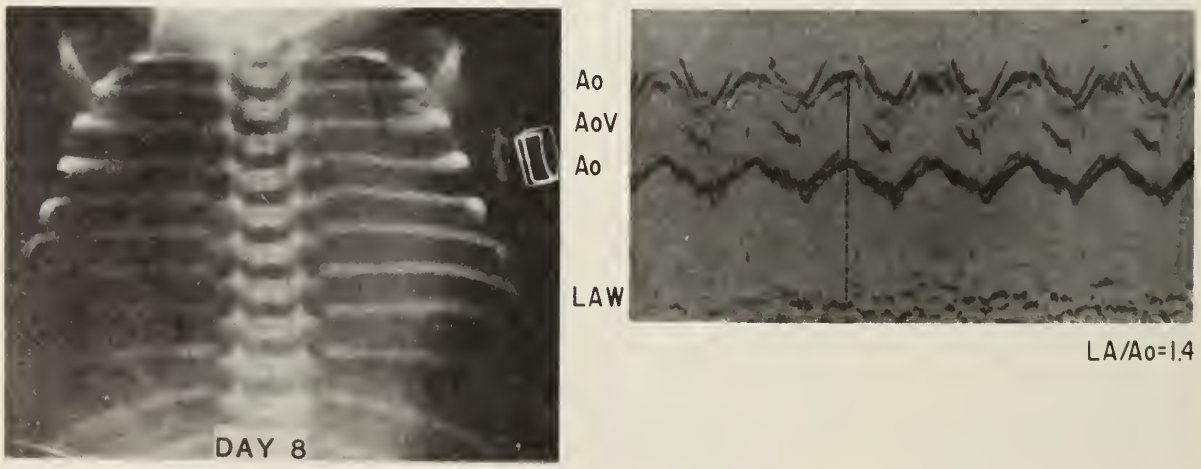


Figure 4.—Correlation of the roentgenographic findings (left) with the echocardiographic evidence of increased left atrial-to-aortic ratio (right).

very helpful in determining the presence of a large-volume shunt. Sequential increase in the cardiothoracic ratio was detected in 75 percent of infants with large-volume shunts. Similarly an elevated LA/AO ratio was seen in approximately 75 percent of infants with large-volume shunts. Using these two modalities together, it was possible to detect 36 of the 37 large-volume shunts in patients in this study.

DR. NYHAN: *Dr. Merritt compiled data on patent ductus arteriosus in order to evaluate our experience. He will summarize this for us next.*

T. ALLEN MERRITT, MD:* Powell[3] first described the surgical ligation of a PDA in a premature infant with progressive heart failure. Until 1972 only seven such cases were reported in spite of the findings of Burnard[4] that 57 percent of premature infants had murmurs characteristic of a PDA. Moss and co-workers reported right-to-left or bidirectional shunting across the ductus in eight of 63 term infants.[5] Similarly, Rudolph and associates[6] found large left-to-right shunts in ten infants with severe RDS. Kitterman and associates[7] recommended cardiac catheterization and ligation in infants with a PDA not responsive to medical management. They proposed that ligation might be the only chance for survival in infants with progressive pulmonary disease resulting from pulmonary hyperperfusion and concomitant RDS. However, only one infant of six in their series with severe RDS and deteriorating pulmonary status survived. Medical management has limitations in patients with this problem. Fluid restriction limits caloric intake in these critically ill infants and may augment a catabolic state. FIO_2 is usually increased and pulmonary compliance worsens as progressive cardiac decompensation occurs. A prolonged period of ventilation with higher pressures and increased oxygen concentrations must contribute to the pathogenesis of bronchopulmonary dysplasia. Despite these problems some centers have advocated medical management alone. Others maintain that aggressive surgical intervention is the most satisfactory approach to premature infants with a patent ductus refractory to medical management. Hall and co-workers[8] have reported such disappointing results that they contend that PDA ligation cannot be justified.

Mortality statistics from 1974 until 1976, a period that should coincide with recent advancements in perinatal care, ranged from an alarming 70 percent mortality to 18 percent[8-18] (Table 2). Our own experience has been very different (Table 3). From January 1, 1976, until December 31, 1976, a hemodynamically significant PDA was found in 25 infants, compromising their recovery from RDS. All of these infants were managed in radiant warmers with crystalloid and colloid calculated initially as 70 ml per kg of body weight in 24 hours and subsequently adjusted to maintain a urine specific gravity between 1.010 and 1.015. Whole blood or packed red cells were given daily to maintain blood balance. Ventilation was carried out in these infants by techniques using low peak inspiratory pressures with prolongation of the inspiratory phase. Twelve infants were medically managed using fluid restriction, digitalis and diuretics. These infants were slightly heavier than the 13 infants in whom more aggressive therapy was required. In these infants the ductus was first detected at seven days of age.

*Fellow in Perinatal Medicine.

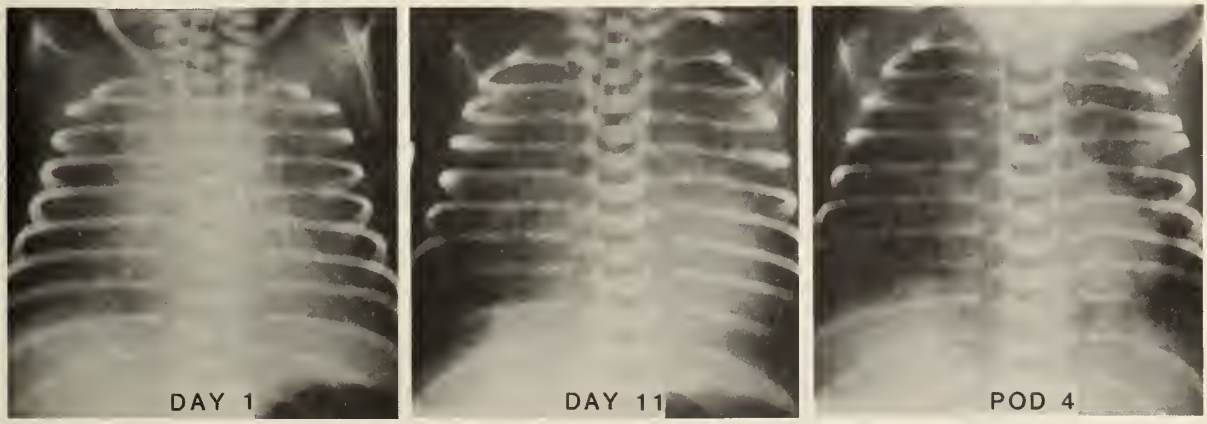


Figure 5.—Progression of roentgenographic findings in a patient with respiratory distress syndrome in whom pulmonary edema developed which resolved following operative closure of a patent ductus arteriosus.

TABLE 2.—*Reported Experience with Surgical Ligation of Patent Ductus Arteriosus, 1974-1976*

Authors	*No. of Cases*	*Mean Gestational Age (Weeks)*	*Mean Body Weight (Grams)*	*Number With Respiratory Distress Syndrome*	*Age (Days)*	*Weight at Operation (Grams)*	*Morbidity*	*Deaths (Percent)*
Murphy (1974)	10	30	..	10	..	1,442	Pneumothorax	50
Zachman et al (1974)	27	30	1,400	22	15	..	Pulmonary hemorrhage, pneumothorax, atelectasis, bradycardia, cardiac arrest, diaphragmatic paralysis	33
Kilman (1974	12	29	..	..	14-56	1,246	..	25
Thibeault (1975)	21	29	1,060	21	13	..	..	38
Neal et al (1975)	5	..	1,260	5	50	..	Bronchopulmonary dysplasia, intraventricular hemorrhage	40
Rittenhouse et al (1976)	11	31	1,325	7	42	1,925	Apnea, atelectasis, pneumonia, respiratory insufficiency	18
Nelson (1976)	32	28	1,000	32	13	..	Pneumothorax, interstitial emphysema, left phrenic nerve paralysis, left chylothorax	41
Williams et al (1976)	20	30	1,400	20	16	..	Pneumothorax, sepsis, intraventricular hemorrhage, hydrocephalus, necrotizing enterocolitis	45
Hall et al (1976)	28	28-30	1,300	28	3-127	..	Bronchopulmonary dysplasia (25 percent), subglottic stenosis, necrotizing enterocolitis, sepsis	47
Clarke et al (1976)	22	30	1,500	20	27	1,300	Pneumonia, bronchopulmonary dysplasia, intraventricular hemorrhage pneumothorax, necrotizing enterocolitis, renal failure	28
Levitsky et al	29	31	1,400	29	28	..	..	70

TABLE 3.—*University Hospital Experience with Infants with Patent Ductus Arteriosus, January 1, 1976-December 31, 1976*

	No.	*Mean Gestational Age (Weeks)*	*Mean Body Weight (Grams)*	*Mean Day Onset*	*Mean Day Closed*	*Mean Days Ventilated*	*Complications*	*Deaths*
Medical Management	12	30-32	1,559	7	23	16	1 death, sepsis, hydrocephalus, spastic diplegia, pulmonary hemorrhage, apnea, bronchopulmonary dysplasia, bradycardia	1
Ligation	6	28-30	1,450	5	9	12 (after ligation, 4.2)	Multiple pneumonia, renal failure, disseminated intravascular coagulation, postoperative wound infection, dehiscence of wound, apnea, bradycardia	0
Indomethacin	7	30	1,380	4	6	11 (after indomethacin, 3.5)	3 transient renal failures, sepsis, apnea, bradycardia	0

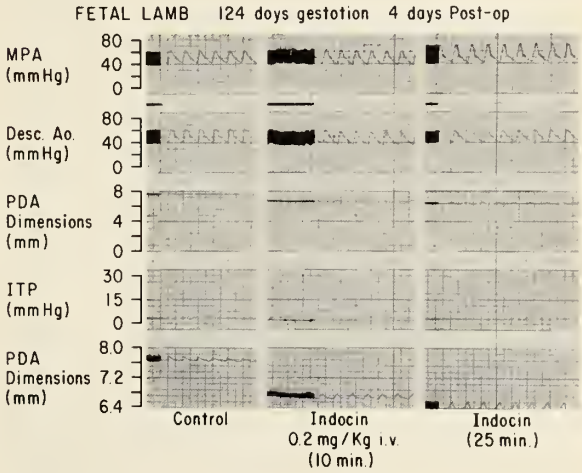
However, ventilatory support was required for an average of 16 days. In six infants surgical ligation was done and in seven others indomethacin was given as part of a prospective trial of pharmacologic closure of the ductus. This group as a whole has done well. Indeed, while these infants represented the sickest and smallest group of infants with worsening pulmonary function related to a left-to-right shunt, these infants required fewer days of ventilatory support and had few complications. During 1976 one infant with PDA died at University Hospital. This 650-gram infant died of a pulmonary hemorrhage four hours before scheduled ligation. Our mortality rate of 4 percent, therefore, compares quite favorably with those reported.

Systematic follow-up has been carried out on these infants including physical examinations, neurological assessment, ophthalmologic and audiologic evaluation, and Bayley Scales of Infant Development. At 3 to 15 months of age, no differences could be appreciated between these three groups. Results of renal function studies in seven infants who received indomethacin were normal as assessed by longitudinal assessment of the creatinine and blood urea nitrogen, and analysis of urine.

DR. NYHAN: *Last year Dr. Friedman and his colleagues reported their experience with a new treatment, the pharmacologic closure of the ductus. Let us turn to Dr. Friedman for an update on ductal physiology and the pharmacologic approach to the* PDA.

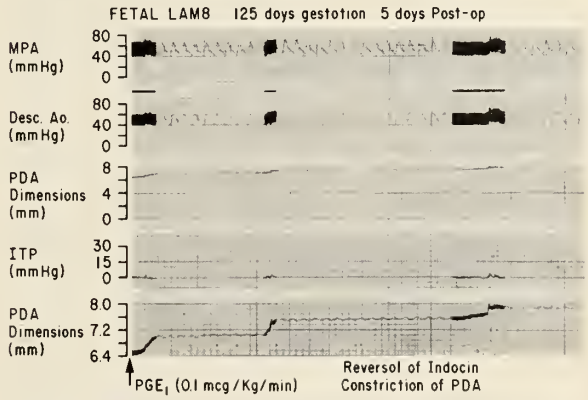
WILLIAM FRIEDMAN, MD:* The ductus arteriosus is a widely patent vessel connecting the pulmonary trunk and descending aorta in fetal life. In the fetus most of the output of the right ventricle bypasses the unexpanded fetal lungs via the ductus arteriosus and enters the descending aorta where it travels to the placenta, the fetal organ of oxygenation. Until recently it was assumed that the ductus arteriosus was a passively open channel during fetal life, and that it constricted postnatally by as yet undefined molecular mechanisms in response to the abrupt rise in arterial oxygen pressure that accompanies the first breath of life. Suggestive evidence now exists that even *in utero* the size of the ductus arteriosus lumen may be influenced by prostaglandins. The effect of prostaglandins on the smooth muscle tone of the fetal ductus arteriosus can be seen in Figure 6. In chronically instrumented fetal lambs the administration of indomethacin, an inhibitor of prostaglandin synthesis, caused constriction of the fetal ductus arteriosus. Prostaglandin E_1 infusion reverses this effect (Figure 7).

The ductus arteriosus is a unique structure after birth since its patency, on the one hand,



ITP = intratracheal pressure.

Figure 6.—Representative experiment in which indomethacin produced profound constriction of the fetal ductus arteriosus. Dimensions of the patent ductus arteriosus (PDA) were measured directly with sonomicrometer crystals while pressures were recorded simultaneously from the fetal ascending aorta, main pulmonary artery (MPA), and descending aorta (desc. Ao). The constriction is best appreciated in the lower panel. A rise in main pulmonary arterial pressure was associated with ductal constriction.



Desc.Ao = descending aorta, ITP = intratracheal pressure.

Figure 7.—Representative experiment in which an infusion of prostaglandin E_1 (PGE_1) restored patent ductus arteriosus (PDA) dimensions to normal after constriction had been achieved with indomethacin administration (0.1 mg per kg of body weight, intravenously). Little change was observed in main pulmonary artery (MPA) pressure during PDA dilatation and aortic pressure rose slightly.

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may result in cardiac decompensation and, on the other hand, may provide the only life-sustaining conduit to preserve systemic or pulmonary arterial blood flow in the presence of certain cardiac malformations. Appreciable left-to-right shunting across the patent ductus arteriosus frequently complicates the clinical course of prematurely born infants. The ductal shunt has been implicated especially in the deterioration of pulmonary function in infants with RDS in whom severe congestive heart failure is often unresponsive to therapy with digitalis and diuretics. Recently, clinical trials at the University of California, San Diego, and at the University of California, San Francisco, have shown that the ductus arteriosus in preterm infants with hyaline membrane disease and cardiopulmonary deterioration can be constricted and closed by the administration of inhibitors of prostaglandin synthesis.

In our initial clinical experience with sick preterm infants to whom indomethacin was given to constrict and close the PDA, a large dose (2.5 to 5 mg per kg of body weight) of the drug was delivered orally or per rectum.[19] Within 12 to 24 hours of drug administration all of the clinical symptoms and physical, radiographic and ultrasound signs attributable to a substantial left-to-right shunt through a PDA had permanently disappeared. In several infants, transient renal dysfunction was shown by a rise in blood urea nitrogen and serum creatinine concentrations and a reduction in urine volume. In the initial clinical trial in San Francisco, salicylates, as well as a smaller dose of indomethacin, were utilized.[19] Salicylates were not found to be particularly effective, and the smaller doses of indomethacin were not associated with transient renal dysfunction.

Prostaglandins are ubiquitous in animal tissues and appear to be formed from polyunsaturated fatty acids. These lipids act throughout the body as local mediators or modulators of physiological functions. Prostaglandins of the E type have a pronounced effect on the ductus arteriosus. It should be stated that pharmacological closure of the ductus arteriosus in preterm infants must still be considered experimental. In our experience, indomethacin was employed in an attempt to constrict and close the ductus arteriosus in preterm infants who would have otherwise undergone surgical ligation of the patent ductus arteriosus. Indomethacin was chosen because of its known potency as an inhibitor of prostaglandin synthetase and its widespread use for diverse medical indications in the adult population. It should be recognized, however, that there exists a large family of drugs that have been shown to interfere with the synthesis of prostaglandins. Studies have not yet been done to identify the single agent with an especially selective action upon the smooth muscle of the ductus arteriosus and little or no action upon other organ systems.

In the combined experience at UCSD and affiliated hospitals, indomethacin has been employed in 33 premature infants. Birth weight ranged from 720 to 2,480 grams. In the 33 infants to whom indomethacin was administered, surgical ligation would otherwise have been done for the PDA. In these infants, therefore, the ductal shunt was responsible for deterioration of pulmonary function, or severe congestive heart failure was unresponsive to administration of digitalis and diuretics. Rarely, severe episodes of apnea and bradycardia provided the indication for closure of the ductus. Each infant was evaluated serially, by the usual clinical and radiographic techniques, and also by analysis of the ultrasound assessment of left atrial and left ventricular dimensions, since the latter determinations have been shown to reflect accurately the augmentation of pulmonary arterial blood flow secondary to left-to-right shunt distal to the atrioventricular valves. In 32 of the 33 infants, the PDA constricted promptly and signs and symptoms were alleviated. In only one infant did the ductus fail to constrict sufficiently to alleviate symptoms, and surgical ligation was required in this infant. In many infants the PDA appeared to reopen between 5 and 14 days after initial drug-induced constriction. One of these babies became sufficiently symptomatic so that indomethacin was administered again with success. The other infants in whom the ductus reopened were asymptomatic and ultimately the PDA's closed spontaneously. Three of the 33 infants died in the hospital of problems unrelated to ductal patency. The causes were pulmonary hemorrhage in a 720-gram baby, sepsis in a 1,200-gram baby and a combination of pneumonia and myocardial infarction in a 1,300-gram infant. Therefore, infants who ordinarily would have undergone ductal ligation were spared a thoracotomy by indomethacin treatment.

Because transient renal dysfunction was observed initially in premature infants in whom indomethacin was being given to inhibit prostaglandin synthesis, and constrict PDA's, a study was undertaken in 14 newborn lambs between one and

six days of age to examine the influence of high and low doses of indomethacin on renal blood flow, glomerular filtration rate and urine flow. The high-dose group received 7.5 mg per kg of body weight of indomethacin intravenously, while the low-dose group received 0.2 mg per kg of body weight of indomethacin intravenously. Each animal served as its own control and each group of animals was compared with a separate control group matched for age and weight in which indomethacin was not administered. The indices of renal function were studied using iodohippurate sodium I 131 and inulin C 14 clearances in conscious, chronically instrumented lambs.

Both high and low doses of indomethacin reduced renal blood flow significantly at four hours, but only in the high-dose animals was blood flow significantly lower than in the control group at 12 and 24 hours. Levels of prostaglandin E determined by radioimmunoassay correlated directly with alterations in renal blood flow. Glomerular filtration rate was unaltered in all groups; urine flow was significantly lower than in the control group at 24 hours only in the high-dose indomethacin group. The filtration fraction rose notably at 12 hours in both high and low dose indomethacin groups. These data suggest that the renal dysfunction observed transiently in some premature infants may be dose-related and support the need to monitor renal function, when indomethacin is administered to preterm infants.

Various experimental approaches have been made in several animal species to elucidate the contractile response of ductus arteriosus smooth muscle. The isolated ductus arteriosus has been analyzed extensively with respect to its responses to oxygen, neurotransmitters, various mediators and hormones. We believe that multiple problems exist with an *in vitro* analysis of the reactivity of smooth muscles of the ductus arteriosus. Accordingly, in association with Drs. Stanley Kirkpatrick and Morton Printz, 42 studies were done from one to twenty-seven days postoperatively in 14 fetal lambs instrumented chronically with PDA sonomicrometer dimension crystals and with pressures determined in the main pulmonary artery and the ascending and descending aorta. Animals were operated on for implantation of the catheters and crystals between 95 and 120 days gestation. This approach to the study of the fetal ductus allows for direct serial measurements of the caliber of the ductus itself, as well as of pressure on all sides of the ductus. Drugs can be infused through a catheter implanted chronically in the superior vena cava so as not to disrupt the monitoring of periductal pressures.

The ductus was dilated maximally *in utero*. Experiments in which prostaglandin E_1 and E_2 were infused intravenously in graded doses up to 1 mg per kg of body weight did not result in altered ductal dimensions. Infusion of prostaglandin F_2 over this same concentration range had no influence on the ductus. We found that alpha and beta adrenergic agonists (methoxamine and norepinephrine, respectively) and adrenergic (phentolamine and propranolol) and cholinergic (atropine) antagonists had no influence on ductal caliber. Acetylcholine infusions caused a mild reduction in ductal dimensions and internal cross sectional area, but concurrently lowered both pulmonary and systemic pressures. Therefore, it was difficult to distinguish between the hydrostatic influence of hypotension on ductal caliber and the direct effect of acetylcholine. Neither angiotensin 1 nor angiotensin 2 infusion, nor blockade of conversion of angiotensin 1 to 2 with the Squibb experimental compound SQ20881 influenced the dimensions of the ductus.

A major finding of these studies was that inhibition of prostaglandin synthesis by a single intravenous dose of as little as 0.01 mg per kg of body weight of indomethacin caused significant PDA constriction. As anticipated, ductal constriction was accompanied by an elevation of main pulmonary arterial pressure with little change in systemic pressures. Infusions of prostaglandin E_1 and E_2 always reversed the constriction and returned ductal caliber to control dimensions. The responses to indomethacin were accompanied by striking reductions in circulating prostaglandin E_2 levels measured by radioimmunoassay. It has not yet been determined if ductal reactivity may be more importantly associated with alterations in prostaglandin synthetase activity within the ductus itself or with changes in circulating prostaglandin levels. Of major interest was the finding of a direct correlation, after fetal administration of indomethacin, between fetal and maternal circulating levels of prostaglandins. These preliminary experimental findings suggest that the prostaglandins may directly influence ductal caliber, and suggest certainly that past theories concerning the mechanisms of spontaneous or delayed ductal constriction must be revised.

The combination of clinical experience and the results of animal experimentation has led to our

current approach to the nonsurgical treatment of preterm infants with threatening PDA. The pretreatment evaluation of infants in whom indomethacin is to be employed is to uncover problems related to bilirubin metabolism, coagulation and renal function. A single dose of indomethacin (0.2 mg per kg of body weight) is then administered intravenously. A meticulous serial assessment is undertaken of cardiopulmonary and clinical status, and laboratory measurements are done to detect bleeding, displacement of bilirubin from albumin, and renal function. Rapid changes in oxygen requirements and the theoretical possibility of retinal arterial vasoconstriction require analysis. If evidence exists that constriction of the ductus has been inadequate, the same dose of indomethacin may be repeated at 12- to 24-hour intervals. If ductal left-to-right shunting remains uncontrolled after a total dose of 0.6 mg per kg of body weight has been administered, then the infant may be considered a candidate for operative ligation. In addition, if after initial closure, the subsequent clinical course indicates that the PDA has reopened and produces cardiopulmonary difficulties, the treatment regimen may be repeated.

We currently employ an experimental intravenously given preparation of indomethacin in our clinical studies which insures delivery of the desired dose. It should be recognized that an orally given suspension or solution of uniform composition does not exist commercially and that potential problems in dosimetry and absorption have not been evaluated critically when the drug is delivered through a nasogastric tube to preterm infants.

In our view, the high morbidity and mortality of premature infants with PDA provides abundant justification for pursuing nonsurgical methods to alter the course of this common problem. One of the major aims of continued clinical studies in this area is to assess the potential complications of the pharmacological approach to constriction and closure of the PDA. It is hoped to provide more appropriate guidelines for the optimal timing of therapeutic intervention.

If results of clinical studies confirm our earlier observations, it will be appropriate to use these agents in infants early in the course of hyaline membrane disease with associated PDA.

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Refer to: Trace elements—Medical Staff Conference, University of California, San Francisco. West J Med 128:223-227, Mar 1978

Trace Elements

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Diseases with associated abnormalities in trace metal metabolism are ubiquitous although actual deficiency states are rare. Dr. Faith Fitzgerald will lead today's discussion about recent progress in the clinical significance of trace metals.*

DR. FITZGERALD:† Trace elements are those elements essential to normal biologic function whose total concentration in the hypothetical 70-kg man is less than four grams. To date, some 17 of these have been described (Table 1), although some are disputed.

The deficiency and excess states of vanadium, tin, molybdenum and silicon are most familiar as depletion states created experimentally in rats. Deficiency states of selenium, chromium and manganese are more likely capable of creating recognizable syndromes in human beings. A toxic excess syndrome has been clearly described for manganese,[1] and seems probable for selenium as well.[2] Gallium, cobalt and fluorine have found use in clinical diagnosis and therapy. The best defined deficiency syndromes involving trace elements are those of copper, zinc and iodine. Iodine deficiency has been well described and needs no further comment here.

Studies in trace elements are carried out in several ways: The usual mode of investigation is by artificial deprivation studies in animals both prenatally and postnatally. More rarely, naturally acquired deficiencies are discerned in animals and man. These are the "experiments of nature," genetic defects and malnutritional states, which give some clue as to the natural requirement for a given element. The third circumstance in which trace elemental deficiencies have been recognized and described are the recently burgeoning "experiments of medicine" or iatrogenic deficiencies. These have been particularly prevalent since the advent of parenteral hyperalimentation.

Zinc

Normal Values

The adult human body normally contains 2 to 3 grams of zinc (Table 2). The adult requirement

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TABLE 1.—*Trace Elements Believed Essential to Normal Biologic Function*

Chromium	Iodine	Silicon
Cobalt	Manganese	Tin
Copper	Molybdenum	Vanadium
Fluorine	Selenium	Zinc
Gallium		

is estimated at 15 to 20 mg per day and is readily obtainable from meats, whole grains, legumes and seafood. Absorption occurs principally in the small intestine. Normal circulating blood levels of zinc range from 80 to 110 μg per dl. Urinary excretion on a normal intake is about 500 ppm in 24 hours.

Function

Zinc is a cofactor or component of more than 70 known enzymes, including aldolases, dehydrogenases, phosphorylases, peptidases, an isomerase, and aspartate transcarbamylase.[3] It is present in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It participates in carbohydrate, lipid, protein and nucleic acid synthesis and degradation.

Deficiency States

Zinc has been known to be essential to the growth of lower organisms since 1869. Deficiency states in animals and human beings have been more recently recognized.[4-9]

Genetic

Acrodermatitis enteropathica is a potentially lethal disease of infants which is characterized by watery diarrhea and seborrheic skin lesions on the acral areas and around body orifices. In 1974 Moynahan[5] reported complete clearing of the skin lesions and restoration of normal bowel function in afflicted infants given supplemental dietary zinc. Studies strongly suggested this genetic disorder to be a selective malabsorption of zinc.[4-6]

Acquired

In 1961 Prasad and co-workers[7] described patients from Iran and Egypt with short stature, pronounced hypogonadism, roughened skin and hepatosplenomegaly. Serum, red cell, hair and urinary zinc levels were all decreased. The zinc deficiency was attributed to a diet high in phytates which bound zinc in the lumen of the gut, leading to a malabsorption of that metal. Because there were no good controls and because there concurrently existed an iron deficiency, there remains some question as to the validity of this syndrome.

More recently, Hanbridge and associates[8] showed low levels of zinc in the hair of children with poor growth and diminished taste acuity in Denver. They speculated that even such relatively affluent children, who were from middle and upper class families, might have dietary zinc deficiency.

In patients with malabsorption and starvation, failure to thrive and poor wound healing have been attributed to an acquired zinc deficiency.[9,10]

An interesting syndrome of decreased acuity of taste (hypogeusia) and impaired olfactory acuity (hyposmia), often following upper respiratory tract infections, in some patients may respond to oral zinc supplements.[11]

Finally, the iatrogenic analogue to acrodermatitis enteropathica has recently been reported in a patient who had been hyperalimented.[12] Because of multiple enterocutaneous fistulae, this young man had been parenterally fed for eight months. He developed alopecia and acrodermatitis-like skin lesions. Serum and hair zinc levels were low, and zinc supplementation led to reversal of the skin abnormalities.

There are some intriguing speculations in the literature about zinc deficient states:[13] Alcoholics with Laennec cirrhosis have long been known to be hyperzincuric with correspondingly low serum zinc levels.[14] Might the hypogonadism, poor wound healing and loss of body hair in patients with cirrhosis be, in part, secondary to zinc deficiency? Similarly, lymphocytopenia is not infrequent in patients with cirrhosis, and has been reported in rats rendered experimentally zinc deficient.[15] A preliminary study in normal volunteers on a low zinc diet suggests that zinc deficiency might lead to a decrease in blood urea nitrogen (BUN) and increase in blood ammonia.[16] Is zinc required for urea synthesis in the liver, and are the low BUN levels and hyperammonemia in severe Laennec cirrhosis a consequence of zinc deficiency? Zinc deficient rats have low plasma vitamin A levels,[17] and both retinal-binding protein and vitamin A levels are diminished in persons with cirrhosis.[18] Is there a connection between these two findings? Obviously, the answers to these questions require further study.

Some researchers believe that the growth retardation, hypogonadism and poor wound healing in patients with sickle cell anemia may be related to the total body zinc deficiency that results from an associated hyperzincuria in these patients. Red

TABLE 2.—*Normal Values for Zinc and Copper*

	Content in 70-kg Man	*Daily Requirement*	*Serum Level*	*Urine Level*
Zinc	2-3 grams	15-20 mg	80-110 μg per dl*	500 μg/24 hours
Copper ..	100 mg	2 mg	79-149 μg per dl† (ceruloplasmin: 20-50 mg per dl)	Less than 50 μg/24 hours

*Increased in hemolysis, tissue breakdown.
Decreased in acute inflammatory states, corticosteroid therapy.
†Increased in biliary cirrhosis, acute and chronic infection, inflammatory rheumatoid arthritis, myocardial infarction, anemias, liver disease, leukemia, lymphoma.

cell zinc concentration is normally higher than that in plasma. There is an increase in urinary zinc in patients with sickle cell anemia, presumably consequent to the greater presentation of zinc to the glomerulus from the hemolytic state. There may alternatively be a specific tubular defect in these patients leading to zinc wasting. According to some investigators,[16] there is a rough correlation between the degree of zinc deficiency and the severity of the sickle cell disease. Perhaps zinc has a role, they speculate, in decreasing hemoglobin binding to red cell membranes. A controlled study of the efficacy of zinc supplementation in sickle cell disease would be illuminating.

Although there are experimental data supportive of poor wound healing in zinc deficient animals,[19] studies attempting to show that supplemental zinc facilitates wound healing in human beings already zinc sufficient[10] have been justly criticized.

Laboratory Studies

The laboratory determination of zinc deficiency is not easy. Serum zinc may be decreased in acute inflammatory states[20,21] or increased transiently in hemolysis or tissue breakdown.[20] Hair levels of zinc, often cited in the literature as a reflection of total body zinc are demonstrative of the *chronic* zinc sufficient or deficient states, and do not reflect more acute changes. Urinary and serum zinc values may be increased in spite of the fact that total body zinc levels are low, as evidenced by the hyperzincuria and hyperzincemia of cirrhosis and hemolysis. Probably the best method of determining zinc deficiency in an individual patient is to check all three: serum, urine and hair zinc values.

Therapy

Doses of supplemental zinc have ranged from 15 mg to several grams per day given orally, usually as zinc sulfide. There is a large therapeutic margin, and zinc toxicity from overdose is rare.

Copper

Normal Values

There are an estimated 100 mg of copper in the hypothetical 70-kg man (Table 2). Total recommended dietary intake is about 2 mg per day, readily available in most meats, especially liver and kidney. There is also ample copper in shellfish, nuts, raisins, legumes and cereals. Normal serum copper in most laboratories ranges between 79 and 149 μg per dl. The normal level of the carrier protein ceruloplasmin is between 20 and 50 mg per dl. There is usually less than 50 μg of copper per 24 hours in the urine.

Function

Copper is an integral component of at least 16 essential metaloproteins in mammals, including cytochrome oxidase, monoamine oxidase, lysyl oxidase, tyrosinase and ceruloplasmin.[22] It may be an important participant in prostaglandin synthesis as well.[23] The major copper-containing enzymes are believed to have their primary activity in the formation of connective tissues, in the function of the central nervous system, and in hematopoiesis in mammals.

Deficiency States

If the functions of copper enzymes are affected in states of copper deprivation, one may predict the metabolic defects and pathologic changes that could occur as a consequence of these deficiencies.[24] Lysyl oxidase participates in cross-link formation in collagen and elastin, so one might expect skeletal and vascular defects to be evident in copper deficiency. Similarly, if dopamine-beta-hydroxylase and cytochrome oxidase require copper, a derangement of catecholamine metabolism and resultant central nervous system dysfunction could be predicted. If an essential ferroxidase cannot be formed without copper, then abnormalities in iron utilization might reflect copper status in an animal or man. Tyrosinase and sulf-

hydryl oxidase deficiencies would logically lead to defects in the formation and pigmentation of hairs.

There is considerable scientific satisfaction in the awareness that a copper deficiency state exists that fulfills all of these predictions.

Genetic

Menkes disease (steely hair syndrome) is a genetic disorder that is manifest clinically between 6 weeks and 6 months of life in infant boys. It was described by Menkes in 1962[25] as an X-linked defect characterized by kinky hair, developmental regression, focal cerebral and cerebellar degenerative changes, seizures, temperature instability, arterial intimal abnormalities and scorbutic bone changes. In these children there were severely diminished copper concentrations in blood, brain and liver.[26] In this genetic circumstance, the copper deficiency evidently results from impaired intestinal absorption of copper and is probably related to defective transport across the serosal cell membrane.[27] Supplementing copper in children with the steely hair syndrome has shown variable results. One may generally achieve an increase in serum copper and ceruloplasmin levels, but little in the way of neurologic improvement is realized.

The best known genetically determined abnormality of copper metabolism is Wilson disease. In this autosomal recessive disorder, there is a defect in the incorporation of copper into ceruloplasmin and an abnormal biliary excretion of copper. This disease, in which the major pathologic changes are consequent upon abnormal tissue levels of toxic unbound copper, is excellently and extensively reviewed elsewhere.[28]

Acquired

A microcytic, hypochromic anemia and neutropenia have been described in patients with severe malnutrition, malabsorption, or total dependence on copper-poor intravenous hyperalimentation. Some infants with profound nutritional inadequacy have concurrent demineralization of bone. Copper deficiency has been credited with participation in both the hematopoietic and osseous abnormalities.

It is known that copper is essential for several electron transfer systems and that its carrier protein, ceruloplasmin (an alpha-2-globulin) has ferroxidase activity.[29] Copper deficient swine fail to absorb dietary iron at a normal rate and a microcytic, hypochromic anemia develops.[30] In these copper deficient animals, mucosal cells of the duodenum accept iron, but do not pass it on to transferrin. Iron is also abnormally retained in reticuloendothelial and hepatic cells, with consequently low serum iron levels in the early stages of copper deficiency.

Since iron must be in its oxidized form to be accepted by transferrin, it is possible that deficiency of iron oxidative activity accounts for the poor absorption and release of iron from storage in the copper deficient state.[31] As copper deficiency progresses, serum iron levels spontaneously rise, but without a necessary improvement in the hematologic status of the animal. This is thought to be because of poor utilization of iron for hemoglobin formation. The nature of this latter defect is not known.

The mechanism of the leukopenia, with decreased bone marrow granulocytosis and "maturation arrest" is also not fully understood.[31,32]

Laboratory Studies

Measured serum copper levels must be interpreted in the light of the clinical presentation of the patient. Hypercupremia is found in many diverse pathologic conditions: biliary cirrhosis, acute and chronic infections, rheumatoid arthritis, myocardial infarction, anemias of a variety of sorts and liver disease.[33] In Hodgkin disease and leukemia, there may be a significant correlation between serum copper levels and disease activity.[34] Hypocupremia, as discussed above, may be genetic (Menkes and Wilson diseases) or acquired. Serum, urine and hepatic copper levels may be required in some cases to assess total body copper status accurately.

Therapy

The treatment of copper deficiency states is with cautious administration of copper supplements, generally 1.25 mg of elemental copper (5 mg of copper sulfate) initially, followed by 0.4 mg of elemental copper (1.6 mg of copper sulfate) per day as maintenance. Excess copper may give rise to an acute toxicity syndrome, with nausea and vomiting, epigastric pain, headache, dizziness, weakness, blue-green diarrheal stools and saliva, acute hemolysis and renal tubular abnormalities.

Summary

The biochemical intricacies of copper and zinc metabolism have long had major appeal only to laboratory investigators or to those working with

the rather rare deficiency states in man. Should it be true that these metals are of pathological significance in chronic disorders such as cirrhosis, sickle cell disease, malabsorption and iron-deficiency anemia, they will become increasingly pertinent to practicing clinicians.

Moreover, physicians using vigorous modern therapies may induce these deficiency states. Therefore, we are even more obliged to identify and repair the depletion of metals which we recognize as trace elements.

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Important Advances in Clinical Medicine

Epitomes of Progress — Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in pediatrics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Cat-Scratch Disease

CAT-SCRATCH DISEASE (CSD) is a disorder characterized by a primary lesion at a site of injury, subacute regional lymphadenitis and mild constitutional symptoms. Complications are rare, the most common being Parinaud oculoglandular syndrome, thrombocytopenia and transient encephalitis. There have been no fatalities in which CSD has been shown conclusively to be the cause. Treatment is generally supportive; antibiotics do not hasten resolution of the disease. In some instances, suppurating fluctuant nodes require aspiration to promote healing. Occasionally, surgical excision of an involved lymph node is required for cure.

Since CSD is benign and self-limited in most cases, it is of interest to clinicians primarily because it is confused with treatable infectious disorders (for example, staphylococci and streptococci infections and tularemia and tuberculosis) which cause regional lymphadenopathy, and other more serious conditions such as lymphomas or sarcoidosis.

CSD should be suspected in a patient with a cutaneous lesion resembling a furuncle and regional lymphadenopathy appearing 1 to 2 weeks after trauma. The diagnosis can be more securely established if (1) there is a history of cat scratch or bite; (2) laboratory studies for other causes of lymphadenopathy are negative; (3) histopathology of a lymph node biopsy specimen is characteristic of CSD, and (4) skin hypersensitivity to cat-scratch antigen can be shown. The presence of three out of four of the above criteria is generally considered sufficient in typical cases. Unfortunately, the etiologic agent of CSD has not been isolated and serological methods of diagnosis are not available. An unequivocal diagnosis of CSD therefore can not be made.

The skin-test antigen is prepared from purulent material aspirated from an affected lymph node. Presumably, it contains the causative agent of CSD, thereby evoking a cutaneous hypersensitivity response in an infected person. Administration and interpretation of the skin test is similar to that used for tuberculin testing.

Recently there has been a growing concern among clinicians that the injection of this human material into man may provide a potential hazard through transmission of slow or incomplete vi-

ruses, or other unknown factors. Indeed, electron microscopic examination of lymph nodes from eight patients with CSD has shown the presence of herpes-like agents in all. The association of viruses from this group with lymphoproliferative disorders in humans and subhuman primates has been recognized for many years. In order to provide a safeguard against possible infection with adventitious agents, it has been suggested that all cat-scratch antigen be exposed to a "sterilizing dose" of gamma radiation (cobalt-60, 2.5 mr) before use. This proposal seems well-founded and reasonable. Although radiation of the antigen reduces the intensity of the cutaneous response in about a third of patients, modification of the criteria for a positive reaction should overcome this problem.

At present, therefore, it is suggested that the diagnosis of CSD can be established in most cases on epidemiological and clinical grounds, together with elimination of other infectious causes through appropriate laboratory methods. This must include examination for the presence of bacteria, both aerobic and anaerobic, fungi, mycobacteria and viruses through smear, culture, serological and skin testing. If this is not sufficient, a biopsy specimen of an involved node should be taken for histological examination. Only under unusual circumstances should it be necessary to carry out a skin test to increase confidence in the diagnosis. Until the safety and reliability of the irradiated skin test material have been established, its use also should be limited.

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The Fetal Hydantoin Syndrome

AN ASSOCIATION between maternal ingestion of hydantoins during pregnancy and a specific pattern of malformation in offspring was described by Hill and co-workers in 1974 and further delineated by Hanson and co-workers, who referred to this disorder as the fetal hydantoin syndrome. The most frequently noted features of this condition include the following: mild to moderate growth deficiency usually of prenatal onset; mild mental deficiency; craniofacial defects which include microcephaly, a wide anterior fontanel in the newborn period, ocular hypertelorism, a broad depressed nasal bridge with a short nose, low set abnormally shaped ears and a broad alveolar ridge; limb defects including hypoplasia of the distal phalanges with small nails, finger-like thumbs and altered palmar creases; umbilical and inguinal hernias; short neck with a low hairline, and anomalies of the rib, sternum or spine. Less frequent anomalies include cleft lip or palate, cardiovascular defects, duodenal atresia, anal atresia and genital anomalies.

Hanson and co-workers recently have reported the results of a prospective study of 35 infants whose mothers had been treated with hydantoin anticonvulsants during pregnancy. Eleven percent had the fetal hydantoin syndrome while an additional 31 percent had some features compatible with the prenatal effects of hydantoins, the most frequent of which was developmental or mental deficiency. At present, a safe dose of hydantoin anticonvulsants has not been established below which there is no increased teratogenic risk.

KENNETH LYONS JONES, MD

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Dangerous or Ineffective Antidotes

MEDICAL SCIENCE sometimes finds that treatments or procedures that have been used for several years actually are ineffective, perhaps even harmful. Such is the case with three "antidotes" that are widely used and suggested by many toxicology texts, first-aid manuals and product labels: the use of table salt in water as an emetic, using acid solutions to neutralize caustic alkalis and the use of the "universal antidote."

Using table salt in water as an emetic has been suggested for decades. Numerous reports of fatalities caused by this seemingly safe emetic can be found in the literature. The ingestion of a hypertonic saline solution will lead to an elevation in serum sodium concentration, particularly in children. This increase in the effective serum osmolarity will promote a shift of water from the intracellular to extracellular spaces—leading to

cellular dehydration, distention of cerebral vessels, and subarachnoid and subdural hemorrhage.

Another harmful procedure is the use of acid solutions to neutralize ingested alkaline caustics. It is true that a weak acid will neutralize an alkali; however, experimental studies have shown that this reaction results in the production of heat severe enough to produce a thermal burn, further damaging the chemically burned mucosal surfaces. Milk, when used as a diluent, will decrease the caustic potential of the alkali while producing no additional heat.

The combination of activated charcoal, tannic acid and magnesium oxide, known as the "universal antidote," has been shown to be ineffective. The charcoal adsorbs the other ingredients making none of them available for their intended use. It should not be recommended or used.

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The Fetal Alcohol Syndrome

THE FETAL ALCOHOL SYNDROME is a pattern of altered growth, morphogenesis and function seen in the offspring of chronically alcoholic women who continue to drink heavily throughout their pregnancy. First set forth in 1973 by Jones and co-workers, the principal features of this disorder include the following: prenatal and postnatal onset growth deficiency, mental retardation with an average IQ of 63, microcephaly, short palpebral fissures, joint contractures, altered palmar crease patterns, cardiac defects and fine motor dysfunction. Approximately 40 percent of infants born to chronically alcoholic women who continue heavy alcohol consumption during pregnancy have serious problems in development. The incidence of serious developmental defects in the offspring of women who drink lesser amounts of alcohol is not known. However, recent evidence suggests that 11 percent of the offspring of women who drink one ounce of absolute alcohol a day during the first trimester of pregnancy have serious problems in development. Nothing is known about the effect of "social drinking" during the first trimester of pregnancy nor are data available on the effect of "binge drinking."

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Reye Syndrome: Evaluation and Treatment of Intracranial Pressure

INCREASED INTRACRANIAL PRESSURE (ICP) secondary to cerebral edema is the major cause of neurological deterioration in patients with Reye syndrome. Increased intracranial pressure should be evaluated early in the course of treatment before irreversible brain dysfunction has occurred. In the presence of pronounced ICP, a lumbar puncture can be hazardous, risking brain-stem herniation. However, when the possibility of meningitis exists, a spinal tap is indicated. Pretreatment with corticosteroids and mannitol may substantially reduce the risk of herniation in these patients. Computerized axial tomography is extremely useful in showing cerebral edema with visualization of diffuse brain swelling and decreased ventricular size, and can usually show if a subdural hematoma is present.

Although independent evaluations should be done in each patient, routine protocol staging will be useful in guiding treatment and in prognosis. Careful monitoring of fluid given intravenously and of osmotic agents such as mannitol (1.5 to 3 grams per kg of body weight given intravenously), urea (1 to 1.5 grams per kg of body weight given intravenously) or glycerol (1.5 grams per kg of body weight given orally via nasogastric tube), and dexamethasone (1 mg per year of age given intravenously every four hours) can be useful in controlling ICP. However, the single most important aspect of reducing ICP is to insure adequate ventilation. Frequent arterial blood gas determinations should be obtained because respiratory intervention may be necessary. Mild hypothermia also may be useful in reducing ICP.

Severe ICP can be monitored with either an epidural or a direct ventricular catheter attached to a pressure transducer. Control of increased intracranial pressure then can be effected using a combination of mannitol and dexamethasone.

Exchange transfusion also seems to be effective in controlling ICP. When ICP remains high despite the above measures, consideration may be given to a near total decompressive craniectomy, which could be lifesaving.

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Sudden Infant Death Syndrome: Research Problems and Treating Parents

A MAJOR ELEMENT of the psychological treatment of parents of a victim of sudden infant death syndrome (SIDS) is providing assurance that the infant's death was unpredictable and unpreventable. To do this, the National SIDS Foundation advocates a four-step program: (1) autopsy, (2) use of the term SIDS, (3) explanation of diagnosis to family and (4) follow-up counseling.

Use of this four-step program has shown the need for another step: immediate tentative diagnosis in the home or the emergency room. Such a tentative diagnosis of SIDS will be "correct" in 85 percent of cases. Even when technically incorrect, it is an appropriate way of saying that the death was natural (only one percent of cases are abuse). Not only should the physician give the parents a cause of death (so that they can say to family and friends "the doctor thinks it's SIDS"), but he should also drop his objective facade by reaching out to them and even crying with them.

After the diagnosis is made, the parents need constant reassurance that they could not have prevented the death. Although SIDS is unpredictable and unpreventable *under our present state of knowledge,* researchers legitimately assume that research will eventually result in prevention. For this reason, research theories have been reported in stories with headlines such as "a new way to stop crib death." These media accounts conflict with the assurance that SIDS is unpredictable and unpreventable, thereby confusing and confounding the parents.

A current example of questionable reporting is the coverage being given to "apnea monitoring to prevent SIDS." Although there is progress in the area of infant sleep and respiratory control, it is uncertain what the relationship of sleep apnea is to SIDS. There is little, if any, proof that monitoring can prevent SIDS. Because of this lack of proof and because psychological and developmental harm can occur from monitoring, committees of the American Academy of Pediatrics and the National Institutes of Health have stated that apnea monitoring should be used *only* in conjunction with research.

Not only is there little evidence that monitoring saves lives, but the literature records the cases of three infants who died while apnea monitoring was being done—one in an intensive care nursery. A theoretical reason for these deaths was given in a recent article in *Science* by a group that believes that sleep apnea causes SIDS. In their conclusion they state, "[apnea monitors] will be ineffective in cases of upper airway apnea, in which respiratory movements increase."

For more than 100 years (from the 1830's to the 1940's), a large thymus was blamed for sudden deaths in infancy. Because this theory appeared to be correct, it was felt that "something had to be done" about large thymuses. Mediastinal radiation was the resulting therapy. The leukemia and carcinoma caused by this treatment should be a stark reminder that "doing something" without scientific basis is dangerous.

NORMAN LEWAK, MD

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Carbamazepine (Tegretol®) in the Treatment of Epilepsy

CARBAMAZEPINE (Tegretol®) has been in use since 1962 as an anticonvulsant drug in Europe and other parts of the world. There has been considerable interest in its anticonvulsant properties because of its relative low sedative actions and the rarity of serious somatic side effects. Carbamazepine was approved in 1974 by the Food and

Drug Administration for marketing in the United States as an anticonvulsant agent in adults. It has not yet received such approval for use in children. Nevertheless, it has been widely used in pediatric practice both in this country and abroad.

Carbamazepine is a tricyclic compound related to imipramine and unrelated structurally to other clinically utilized anticonvulsant agents. Most reports have indicated that carbamazepine is an effective anticonvulsant in grand mal, psychomotor and focal motor seizure disorders. Petit mal seizures are apparently not influenced by therapy with carbamazepine. The major adverse side effect reported has been bone marrow aplasia, but this is a very rare occurrence. Transient side effects often seen include dizziness, diplopia and blurred vision. Urticaria rashes have been noted.

Dosage levels range from 10 to 25 mg per kg of body weight per day in two to three divided doses. The drug is provided as a scored 200 mg tablet. Therapeutic blood levels commonly range from 5 to 15 mg per ml. Frequent complete blood counts are prudent. If the leukocyte count falls below 3,500 per cu mm, use of alternate drugs should be considered.

Carbamazepine is a major new addition to the therapeutic armamentarium of anticonvulsants. Because its sedative effects are less than those of phenobarbital and it does not cause the cosmetic problems phenytoin sodium (Dilantin®) does, it is likely to be used increasingly in the treatment of seizure disorders.

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Laparoscopy in Infancy and Childhood

WITH THE DEVELOPMENT of the Hopkins quartz rod lens system, laparoscopy in infancy and childhood is now practical. The procedure requires general anesthesia with relaxation. The viewing telescope is introduced through the umbilicus, and the resulting scar is usually invisible.

Laparoscopy is most valuable for inspection and taking biopsy specimens of the liver. In addition, if jaundice is present, a needle may be introduced through the liver into the gallbladder, and an operative cholangiogram done as described by Gans; in this way, laparotomy can be avoided and biliary atresia can be ruled out in cases of neonatal hepatitis.

Another frequent indication is lower abdominal pain in adolescent girls when the differential diagnosis includes ruptured ovarian follicle, ovarian cyst, salpingitis and appendicitis.

In cases of intersex it is possible to see and take biopsy specimens of the internal genitalia without the need for laparotomy.

Four series of laparoscopies in infants and children, totaling 167 cases, have been reported without complications.

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Childhood Hypertension

HYPERTENSION IN CHILDREN and adolescents is a subject receiving increasing attention. Until recently, there was little information about the distribution of blood pressure levels in these age groups. However, under the auspices of the National Institutes of Health, blood pressure grids (akin to height and weight grids) have been developed, giving percentiles for the distribution of blood pressure in normal boys and girls 2 to 17 years old. Data for these grids were derived by auscultation in the right arm with appropriately sized blood pressure cuffs and with subjects in the sitting position. Throughout the entire age group the fourth phase or muffling sound was selected to represent diastolic pressures. The grids were developed from studies in more than 11,000 children and will soon be available for distribution.

The National Heart, Lung, and Blood Institute sponsored the Task Force on Pediatric Hypertension (Chairperson, Dr. Sidney Blumenthal) to review the state of the art and to make specific recommendations for health care professionals. The report was published as a supplement to *Pediatrics* in May 1977. Among its recommendations were the following: Blood pressure meas-

urements should be included in the physical examination of all children 3 years old and older as part of their continuing health care. These measurements should be plotted on grids. In a child in whom levels exceed the 95th percentile on four occasions, evaluations should be done taking into account the parents' history (hypertension or its complications), the health and blood pressure levels of siblings, the patient's history and findings on physical examination of the patient. Guidelines for pharmacotherapy in stepped graduations are provided.

Finally, the *Plan for Hypertension Control for the State of California,* adopted in 1976, includes a segment dealing with children and adolescents. Further information can be obtained from Dr. Harold Mozar, Chief, Chronic Disease Control Section, State of California Department of Health.

ELLIN LIEBERMAN, MD

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Hypothyroid Screening of Newborns

CONGENITAL HYPOTHRYOIDISM probably is the most frequently occurring, preventable, congenital cause of mental retardation. Its incidence, about one in 5,000 births, is about twice that of phenylketonuria—which already is subject to mandatory newborn screening. Screening programs in North America have screened about 700,000 newborns and detected permanent congenital hypothyroidism in 166 of them; thyroid dysgenesis was found in 85 percent of the 166, inborn defects in thyroid hormonogenesis in 10 percent and hypothalamic-pituitary hypothryoidism in 5 percent. In only seven of the 166 infants was the condition suspected on clinical grounds before six weeks of age. Most of the screening programs now are testing filter paper blood spots (as used for phenylketonuria screening) for thyroxine content by radioimmunoassay and following this with a thyrotropin content radioimmunoassay on samples with the lowest 3 percent of thyroxine values. Infants with a low blood thyroxine level and a high thyrotropin level are recalled immediately for serum testing and treatment.

Infants with the lowest 1 percent of thyroxine values and low thyrotropin levels are retested at six weeks or the physician of record is notified of the low thyroxine and thyrotropin values—which may indicate prematurity, low serum thyroxine binding globulin level or hypothalamic-pituitary hypothyroidism.

Treatment of involved infants now is begun within four weeks of birth. Evaluation and preliminary IQ testing of treated newborns (after 12 months of treatment) suggests normal development. The cost of the program is $1 to $2 per infant screened, or $5,000 to $10,000 per infant in whom congenital hypothyroidism is detected. Without early diagnosis and treatment, special education is required in about 70 percent of hypothyroid infants at an estimated cost of $30,000 per infant, and prolonged custodial care is required in 20 percent.

Newborn screening programs for congenital hypothyroidism, therefore, are effective in detection of the disorder and facilitation of early treatment, and are cost effective. Preliminary information suggests that early treatment prevents mental retardation and minimizes the impact of congenital hypothyroidism on public budgets for care and rehabilitation of the mentally handicapped.

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The Lung Profile: Fetal Lung Maturity

FINDINGS FROM recent studies have shown that the maturity of the lungs in a fetus can be determined using various measurements of phospholipid indicators in amniotic fluid. These phospholipids originate from surfactant produced in fetal lungs and are secreted into amniotic fluid during gestation. They include lecithin and sphingomyelin (as the L/S ratio), the percentage of disaturated lecithin (which increases during gestation to 50 percent at maturation and as high as 70 percent at term), and percentages of two acidic phospholipids, phosphatidyl inositol and phosphatidyl glycerol. These latter two phospholipids

are essential in stabilizing lecithin in surfactant. Before this new concept evolved, it had been thought that lecithin was *the* surfactant instead of *a* surfactant—as our information now shows it to be.

These measurements of phospholipids are called the lung profile. They are combined on a graph interpreted according both to weeks of gestation and to whether the lung is immature, premature, transitional, borderline mature, mature or postterm. The lung profile has been especially valuable in the management of problem pregnancies. Use of the lung profile also has made it possible to virtually eliminate intermediate, low L/S ratios where subsequent babies do not have respiratory distress syndrome (RDS), giving a clear picture of the state of lung development. Of special importance is the finding that in infants born to mothers with gestational diabetes (diabetes A) there may be a delay in maturation of the phosphatidyl glycerol. Consequently, awaiting the appearance of phosphatidyl glycerol is a way of assuring that infants born to mothers with diabetes will not have RDS.

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Congenital Diaphragmatic Hernia

EVIDENCE IS ACCUMULATING that some babies born with a large, congenital diaphragmatic hernia who do not survive with currently accepted management may be saved by special treatment directed to increasing pulmonary blood flow. These are infants with a fairly severe diaphragmatic hernia who, after it is repaired, do well with adequate oxygenation for 6 to 24 hours and then become hypoxemic and die. In some such patients differential cyanosis was noted, indicating right-to-left shunt through the ductus due to pulmonary artery hypertension and deficient pulmonary blood flow, or persistent fetal circulation. Infusion of vasodilator substances such as chlorpromazine, tolazoline, or acetylcholine sometimes accompanied by ligation of a patent ductus apparently has helped in a small number of cases.

Additional experimental and clinical work is under way to establish the place of manipulation of pulmonary blood flow in the management of severe congenital diaphragmatic hernia.

DAVID L. COLLINS, MD

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EDITORIALS

Thoughts About Geriatrics

THE SHEER NUMBERS of persons who live to reach the geriatric years in the United States have steadily increased over the last several decades. Persons in the geriatric age group are now beginning to represent a very significant portion of the total population and this is having important political, economic and social consequences which are only starting to become evident. One can already sense a growing public concern with the problems of the elderly in this nation—a reflection of the political, economic and social pressures they generate. As with so many things these days, medicine and health care seem to be at a central focus and the issues of geriatric medicine are receiving more attention.

Alex Comfort elsewhere in this issue draws attention to geriatrics and asks if it is "the missing discipline." This could be so. On the surface at least it would seem reasonable that if we have pediatrics as a specialty at one end of life's span, there might be a place for a specialty of geriatrics at the other. But to many people it is not clear that such a specialty is needed, or what would be its special subject matter distinct from general and specialized medical care as we know it today. Yet one senses the beginning of a push to develop geriatricians and geriatrics as a specialty, reminiscent of the push which so successfully developed family physicians and family practice in the last decade or so. Just as was the case with family practice and primary care, there now seems to be a growing belief or perception that elderly persons may not be receiving the amount or kinds of care they need from the present spectrum of specialists.

In what ways might geriatrics differ from general and specialized medicine as known today? There is of course the possibility, or even the probability or the fact, that diseases may present differently in the elderly, or that drugs may act differently or require different dosages in elderly patients. But it can be argued that physicians who now see adult patients know these things. Are there other perhaps more substantive or even subtle differences?

Leaving aside the political, economic and social pressures being brought on by the increasing numbers of the elderly, it is a statistical fact that the amount of health care needed at least doubles in the geriatric years and this is coming to be of great importance to both medicine and society. And indeed the kind of care needed may be somewhat different. The elderly bear the scars of a lifetime of physical, mental and emotional trauma, and as part of the aging process are more apt to suffer from various chronic ailments and a lessened capability to cope.

Perhaps it is indeed time that we pay more attention to the implications, for medicine and for health care, of life expectancy now extending well into the eighth decade of life. Maybe more attention should be given to the biologic continuum of aging from birth (or conception) to death in the later years. This is a natural process about which we know less than we should. There is also the human side of aging—what it means to become elderly—impaired vision, hearing, mastication; the ever more rapid passage of time; lessened physical stamina; often diminishing intellectual capacity and emotional drive. Then there is the countervailing richness of experience and perspective. Could it be that there is some substance in all this for a science or discipline of geriatrics, and perhaps even for some specialized patient care based on knowledge and skills derived from such a discipline? Then in the health care of the elderly it is evident that there is a lessening of curing and a greater need for and reliance upon caring. The curing interventions become less frequent, and often are less likely to be successful, while the support and caring functions increase in importance, and can even reach their highest expression in the care of the dying.

In many ways it seems that medicine may reach its own true maturity in the care of the elderly. The patients are certainly mature and often can contribute great wisdom to their own care. The biologic processes with which medicine is concerned can be viewed in the perspective of their full maturity, particularly as our knowledge of them develops further. The curing and caring functions in health care achieve a balance that wisdom and maturity surely can bring. Quality of life takes on new meanings. And the sheer numbers of the elderly increase ever year.

Viewed in this way, geriatric medicine—whether specialty or not—becomes a kind of

supreme expression of the art and science of our profession, and one which our profession and, yes, the public can foster, nourish and nurture for the good of all concerned.

—MSMW

Prevention of Meningococcal Disease: Practice and Prospects

In 1977 the occurrence of meningococcal disease in the United States, at least as reported through official public health channels, was close to a record low: 1,752 cases were reported, up only slightly from the five-year median of 1,355 cases reported annually from 1972 through 1976.[1] In spite of this small number of cases, meningococcal infection continues to evoke a deep fear, sometimes bordering on hysteria, in the circle of acquaintances of a person stricken with the disease, and also evokes a wide range of responses on the part of physicians in dealing with persons so exposed.

A number of factors can be cited that undoubtedly contribute to physician uncertainty in managing persons exposed to a patient with meningococcal disease. First, the infrequency of the disease makes it statistically unlikely that any single physician will need to confront the issue more than once every five or ten years. Second, the degree of risk among exposed persons under nonepidemic conditions has only recently been defined with some degree of accuracy. Third, authoritative recommendations for the chemoprophylaxis of meningococcal infection have been frankly contradictory.[2,3]

For all of these reasons, the findings of Juels and his colleagues—elsewhere in this issue—describing their observations on the management of meningococcal disease in California should come as no great surprise. Particularly worthy of note was the finding that chemoprophylaxis of some kind was given to 68 percent of household contacts, but also to 83 percent of nonhousehold contacts. Penicillin, a drug known to be ineffective in eradicating the meningococcal nasopharyngeal carrier state, was by far the single most popular drug given for chemoprophylaxis.

These data are particularly relevant, since they strike, at it were, very close to home. The aggregate performance of California physicians in this situation is, however, not substantively different from that described by the Meningococcal Disease Surveillance Group for the year 1974 in the entire country.[4] They identified a similar series of problems in that chemoprophylactic drugs were often given too late to achieve maximal preventive benefit, inappropriate drugs such as penicillin were used in a high proportion of instances, or chemoprophylaxis was provided to persons whose degree of contact was such that there was probably no increased risk of meningococcal disease.

Therefore, it seems appropriate to restate, briefly, the rationale and recommendations for chemoprophylaxis of meningococcal disease. An increased risk of meningococcal disease has been clearly shown for household contacts of a case, even under nonepidemic conditions.[2,5] Although the available data do not permit precise quantitation of the degree of risk, virtually all studies point to the fact that the degree of risk in exposed household contacts is several hundred or more times greater than the risk of the general population. Consequently, chemoprophylaxis, directed at household contacts, particularly children, seems eminently justifiable.

Drugs known to be ineffective for meningococcal prophylaxis include penicillins, ampicillin, erythromycin, and tetracyclines with the single exception of minocycline. The vestibular reactions reported to occur after the administration of as little as a single 100-mg dose of minocycline have, however, imposed severe limitations on its utility in meningococcal chemoprophylaxis. The currently recommended regimen is rifampin, 600 mg every 12 hours for four doses in adults, 10 mg per kg of body weight every 12 hours for four doses in children 1 to 12 years old and 5 mg per kg of body weight per dose every 12 hours for four doses in children less than 12 months of age.[10]

No chemoprophylactic regimen is 100 percent effective, and occasional failures undoubtedly will occur. The "failure" described by Khouri-Boulos,[5] however, was probably due to reacquisition of Neisseria meningitidis from a baby-sitter who had not received rifampin chemoprophylaxis.

The decision to provide chemoprophylaxis to family contacts of a case should be made promptly, without resorting to prior nasopharyngeal cultures. Munford and his colleagues,[6] studying the occurrence of secondary cases in the major epidemic in Sao Paulo, Brazil, in 1972, found that 33 percent of secondary cases occurred within the first four days after the initial or index case was diagnosed. Furthermore, a nasopharyngeal

culture is only a sampling procedure, at best, and might miss meningococci even if present. Finally, one could argue with some reason that the person in whom a culture is negative may be at greater risk of disease than the person who is already carrying meningococci in an asymptomatic fashion, since the carrier state is generally an immunizing event.

Perhaps the greatest psychological pressures for chemoprophylaxis are brought to bear in the case of nonhousehold contacts, particularly classroom contacts. Utilizing the opportunity provided by the recent epidemic in Brazil, Jacobson and his colleagues[7] convincingly showed that there was no significantly increased risk associated with classroom exposure to a student with meningococcal meningitis; thus, no recommendation for chemoprophylaxis of classroom contact can be made.

Science ends at this point with regard to chemoprophylaxis, and the art of medicine must take over. Recognizing the almost hysterical fear that sometimes occurs in persons exposed to this disease, the understanding and perceptive physician may sometimes elect, quite justifiably, to provide chemoprophylaxis for psychological reasons alone.

The companion report in this issue by Oill and her associates provides a vivid illustration of a "household" outbreak and illustrates what can happen when an unusually invasive strain is disseminated into a susceptible population. Such dramatic outbreaks are fortunately infrequent, but invariably one wonders just what it was about that particular strain of group B Neisseria meningitidis that made it so highly invasive? Are there detectable differences between strains with obvious disease producing potential and the other strains that so many of us carry around harmlessly (perhaps beneficially) in our nasopharynges? Answers to this question are slowly emerging, and appear to be distinctly affirmative. Both Frasch and Chapman[8] and Gold and co-workers[9] have been investigating antigens of Neisseria meningitidis other than the serogroup (A, B, C, and so forth) capsular antigens. Subcapsular protein antigens, localized to the outer membrane of the cell envelope, have been identified, at least some of which are common to all the usual serogroups of meningococci.

Work recently reported by Griffiss and associates from Walter Reed Army Institute of Research[10] suggests that one or more of such subcapsular antigens may be associated with invasiveness or epidemic potential. Therefore, certain antigens are almost invariably present in meningococci isolated from cases, but generally absent in organisms isolated from healthy carriers. These findings raise the possibility that protein subcapsular antigens may ultimately form the basis for another approach to immunization against meningococcal disease. Although polysaccharide vaccines against both group A and group C meningococci have been highly effective, no satisfactory polysaccharide vaccine directed against group B meningococci has been developed. If antibody directed against protein subcapsular antigens can be shown to be protective, it may prove possible to prepare vaccines containing such protein antigens that will, in effect, protect against meningococci of all serogroups. Such an approach seems well worth pursuing.

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Public Views of NHI

During the month of October 1977 the Department of Health, Education, and Welfare conducted an intensive outreach effort to solicit the public's views of national health insurance (NHI). Public hearings were held in every state and more than 8,600 persons and organizations provided oral or written comments. Health professionals and professional organizations and other medical groups were well represented, as were the elderly, the general public, insurance companies and many others. A report of this considerable effort has recently become available.[1]

A genuine attempt seems to have been made to involve all who should or might want to be involved. The result was something like a national town meeting with all the various interests presenting their views on more or less equal footing. The wide spectrum of opinions, some informed and some probably not so well informed, is candidly revealed. Few if any clear directions or recommendations emerged, and it is to be hoped that our political and bureaucratic leadership takes heed and proceeds cautiously.

In a way this approach seems like a breath of fresh air. Those most concerned and interested in this complex problem were being asked rather than being told by government, and the response has the ring of truth. It is possible that a first step has been taken toward solving a major social problem by seeking something approaching a national consensus as opposed to arbitrary legislative fiat or perhaps an imposition of the will of a determined minority. In this exercise one can see the germ of a new more democratic and more participatory approach to solving some of the more difficult social and economic problems of modern America, an approach that will involve all those who should probably be involved in decision making and one that is in the tradition of true participatory democracy which is one of our nation's great heritages. It is to be hoped that the proponents of this approach will not be discouraged by the lack of clear direction or recommendation for NHI at this time. This is simply the way it is. But this outreach effort can be viewed optimistically as an essential first move toward a consensus that will truly reflect the will of the people on this important matter. —MSMW

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Patent Ductus Arteriosus

THAT A PERSISTENTLY patent ductus arteriosus can produce problems in preterm infants is one of the few clearly established facts in the field. Although complete data are not yet available, the incidence of prematurity is about 15 per 1,000 live births and of these infants about half (8 per 1,000 live births) have a patent ductus arteriosus. The recognition, significance and management of a patent ductus arteriosus are still topics of vigorous debate among neonatologists and pediatric cardiologists. The Specialty Conference in this issue has presented some of the specific views of the group in San Diego. These views, and some of the concepts presented, do not necessarily agree with those of others working in the same field; this points out the lack of agreement and standardization that exists. These authors have touched on a few of the questions that are currently posed, but unfortunately have not been able to come up with any new clear answers or unifying recommendations. They also have not touched on several very important topics. This failure is not completely for lack of attempt at illuminating the problem, but rather reflects our sadly incomplete understanding of the physiology and pathophysiology of the ductus arteriosus.

It is unfortunate that Dr. Gluck feels that pediatric cardiologists are not an integral part of the overall care of small preterm infants in the intensive care nurseries but rather should be invited only in a consultant role. This is understood when one considers the high incidence of patent ductus arteriosus and that the major advances in diagnosis and management of infants with this disorder come from cardiologists. Even more in keeping with a tandem approach to management of all preterm infants is the not infrequent occurrence of the very subtle signs of a patent ductus arteriosus (and occasionally no signs) as described. These may well require the early use of noninvasive techniques, such as echocardiography, as well as possible invasive techniques, such as retrograde aortography. These both require the services of pediatric cardiologists.

Although important, recognition of the presence of a patent ductus arteriosus with either obvious or subtle signs is not as critical as recognition of the significance of the hemodynamic alterations produced by the left-to-right shunt through the patent ductus arteriosus. Duration and volume of murmurs are notoriously misleading, pulse volume and pulse pressure are frequently increased in normal premature infants, and many of the clinical signs typical of patent ductus arteriosus in older children are not present in premature infants. Echocardiographic assessment of left atrial size as a reflection of shunt magnitude has been a valuable addition to management. As with all individual components of diagnosis, however, an increase in left atrial size can be easily misread or misinterpreted. Changes in blood volume without a shunt could well affect left atrial size. Likewise, variations in ventilator pressures affect the measured left atrial size. An increased left atrial dimension, therefore, does not always mean a patent

ductus arteriosus and conversely a normal left atrial dimension can well be found in the presence of a large shunt.

Because of some of these shortcomings, Dr. Higgins has attempted to introduce a different approach to the assessment of the magnitude of left-to-right shunt and the effects thereof. The data of sequential changes in heart size and pulmonary vascularity are interesting and point out the dynamic nature of the condition and the fallibility of relying on a single observation as an index of severity. In a significant proportion of infants, however, increasing cardiothoracic ratios are not seen and, in the hands of many radiologists and pediatric cardiologists, the degree of plethora in the face of intrinsic pulmonary disease cannot be read with accuracy as he suggests. No doubt the techniques described can and will be refined further.

Once again we must stress that no single clinical or other investigation stands on its own. The integration of both x-ray and echocardiographic evaluation with clinical assessment is mandatory.

Animal experimentation has established clearly that inhibition of prostaglandin synthesis by such pharmacologic agents as indomethacin produces constriction of the ductus arteriosus of fetuses and newborns. Application of this principle to the clinical management of preterm infants with persistently patent ductus arteriosus is still a subject of some controversy. Does indomethacin in fact have a high success rate in closing or constricting the ductus arteriosus sufficiently to reverse heart failure in these infants? The present series, as well as our own, indicates that this is in fact so; other investigators, however, have reported a somewhat lower success rate.[1] If nearly complete success is not assured, are the potentially harmful side effects worth risking? Are these potential side effects in fact a real problem? Are the effects on urine production invariable and what are they due to? Most important, is the transient depression of renal function associated with subsequent permanent damage to the kidney? Conversely, is indomethacin in fact safer than the drugs currently used in the management of congestive heart failure? Diuretic agents, used with impunity, have been studied as little as indomethacin in preterm infants.

All of these, and many other questions, require answering before we can safely recommend indomethacin as the therapy of choice for all infants under all conditions. Until then, carefully controlled evaluation of the efficacy and the effects, both short-term and long-term, must continue.

Dr. Friedman has addressed several of these problems; specifically, the effects of indomethacin on renal function have been investigated in experimental animals. His experimental data on the reduction of renal blood flow are not in agreement with our own, probably because of the measurement techniques used. Our studies with radionuclide labeled microspheres, which measure flow directly, show no change in renal blood flow nor in intrarenal distribution of blood flow.[2] Since prostaglandins affect renal function in many other different ways, we must look to other mechanisms for the reduction in urine volume seen with the clinical usage of this drug. That there is a disturbance of renal function in a high percentage of treated infants is clear; however, this is not an essential side effect of the drug and when it does occur it is only transient. As indicated by Dr. Merritt, long-term follow-up is required and in the few infants so followed no effects were noted.

Will indomethacin turn out to be the drug of choice or will a more selective agent be found? If indomethacin in fact is to be used, what is the appropriate dose? When during the course of the disease should it be given, and when should it be repeated or, in fact, should it be repeated? Little is known about the pharmacokinetics of indomethacin in preterm infants but it is likely that the half-life is considerably longer than that in the adult. Is the well-known reduction of platelet aggregation associated with an increased incidence of hemorrhage in the preterm infant? Does indomethacin have a significant effect on other organs that we are not able to detect readily? What is the interrelationship of the inhibition of prostaglandin synthesis and the sympathetic nervous system, particularly in relationship to the control of systemic vascular beds? This latter question is of great significance since these are stressed infants in whom the sympathetic nervous system is likely to be highly activated. It is clear that only well-controlled, large scale studies will provide answers to these questions.

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CASE REPORTS

Refer to: Levine GA, Williams DE, Hershman JM, et al: Graves hyperthyroidism following myxedema in a patient with recurrent carcinoma of the colon. West J Med 128: 240-244, Mar 1978

Graves Hyperthyroidism Following Myxedema in a Patient With Recurrent Carcinoma of the Colon

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CHRONIC LYMPHOCYTIC THYROIDITIS (Hashimoto thyroiditis) has been increasing in frequency in the United States and now is the most frequently seen thyroid disorder, probably accounting for most instances of idiopathic acquired hypothyroidism.[1] Hypothyroidism following hyperthyroidism is not unusual, but the reverse situation, that of hyperthyroidism following hypothyroidism, is rare. We report a case we have followed during transition from idiopathic hypothyroidism to Graves disease with hyperthyroidism to a euthyroid state over a seven year period. The relationship of the development of hyperthyroidism in this man to recurrent carcinoma of the colon is also of interest.

Report of a Case

In a 58-year-old white man hyperthyroidism developed in 1973, four years after well-documented hypothyroidism. His illness began in 1969 with a six-month history of easy fatigability, weakness, stiffness and cramping of his muscles, and a 25-pound weight gain. He had not received goitrogenic drugs or iodine. There was no family history of thyroid disease; one of seven siblings died of stomach cancer and another of an unknown type of cancer.

On physical examination, the pulse was 75 beats per minute and blood pressure was 110/85 mm of mercury. Dry skin, puffiness around the eyes, delayed relaxation of the deep tendon reflexes, and swelling, induration and non-pitting edema of the muscles were noted. The thyroid was not enlarged or tender and was of normal consistency. Figure 1 depicts the serum thyroxine (T_4) values over a seven-year period. Initially the protein-bound iodine (PBI) was 2.0 μg per dl with two repeat values of 1.9 μg per dl, and a T_3 resin uptake was 22.4 percent (hypothyroid range). Thyroid radioiodine uptake was 2 percent at 6 hours and 0 at 24 hours. Serum cholesterol was 330 mg per dl, and creatine phosphokinase was 17 sigma units (normal 0 to 12). An electrocardiogram showed low voltage of T waves in I, V5 and V6. To obtain faster improvement of his myopathy, the patient was treated with triiodothyronine (Cytomel®), 75 μg per day for eight days, along with desiccated thyroid, 180 mg per day; within ten days he noted pronounced improvement and lost 10 pounds. He remained euthyroid on 180 mg of desiccated thyroid per day. In February 1971 he complained of double vision, tearing of his eyes and limitation of upward gaze on the left, and in September 1971 he stopped the thyroid medicine because of worsening eye symptoms, nervousness and fatigue. In December 1971 proptosis measured 20 mm bilaterally. The eye symptoms subsided over the next 18 months and he remained euthyroid with no medications being given. Serum T_4 iodine was 5.4 μg per dl (normal 2.9 to 6.5) in December 1971 and 5.7 μg per dl in March 1972, six months after thyroid therapy was discontinued. Thyroid radioiodine uptake was 8 percent at six hours (normal 5 percent to 25 percent) and 22 percent at 24 hours (normal 10 percent to 40 percent) in March 1972.

In August 1973 the patient reported a two-month history of nervousness, tremor, palpitations, weakness, easy fatigability and a 20-pound weight loss. On examination the patient was noted to be thin and nervous with a pulse of 110 beats

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Submitted, revised, June 20, 1977.

Supported in part by the Medical Research Service of the Veterans Administration and USPHS Grant HD-7181.

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per minute, fine tremor, lid lag, mild chemosis, and restricted extraocular movement with diplopia on upward and lateral gaze bilaterally. Proptosis measured 17 mm in the left eye and 15 mm in the right eye. There were proximal muscle weakness and hyperactive reflexes. The thyroid gland was minimally enlarged, nontender, and firm without nodules. Pretibial dermopathy was not present. Serum T_4 was 14.5 μg per dl and serum total T_3 (by radioimmunoassay) was elevated to 300 ng per dl (Figure 1). The radioiodine uptake was 55 percent at 6 hours and 59 percent at 24 hours, and did not suppress after six days of therapy with triiodothyronine, 100 μg per day. Bioassay of serum for thyroid-stimulating hormone (TSH) and long-acting thyroid stimulator (LATS) by the McKenzie mouse assay was negative, and TSH by radioimmunoassay was less than 1 μU per ml. Antibody testing (Table 1) showed positive anticytoplasmic antibodies and positive antimicrosomal antibodies, negative anticolloid and negative antithyroglobulin antibodies. Thyrotropin-displacing activity was detected in immunoglobulin concentrates of the serum using ^{125}I-labeled bovine thyrotropin and human thyroid membranes.[2]

Concomitant with the development of hyperthyroidism, there was recurrence of an adenocarcinoma of the colon without metastases. Adenocarcinoma of the colon had been resected in 1952 and 1958, and metastatic lesions on the abdominal wall had been removed in 1953 and 1959. The

TABLE 1.—*Tests of Antithyroid Antibodies*

Date	*TRC-T_g*	*Cyto*	*Colloid*	*Microsomal*	*TDA*
9-10-73	<1:10	++	0	1:400	+
10-5-73	<1:10	+	0	1:400	..
10-11-73	<1:10	+	0	1:400	..
12-3-73	<1:10	+	0	1:100	..
12-14-73	<1:10	+	0	1:100	..
12-18-73	<1:10	+	0	1:100	..
1-4-74	<1:10	0	0	1:100	..
3-19-74	<1:10	0	0	1:100	..
3-29-74	<1:10	0	0	1:100	+

TRC-T_g = hemagglutination of thyroglobulin-coated tanned red cells
Cyto = antithyroid cytoplasmic antibodies detected with immunofluorescence
Colloid = colloid antibodies detected with immunofluorescence
Microsomal = hemagglutination of microsomal-coated red cells
TDA = thyrotropin-displacing activity

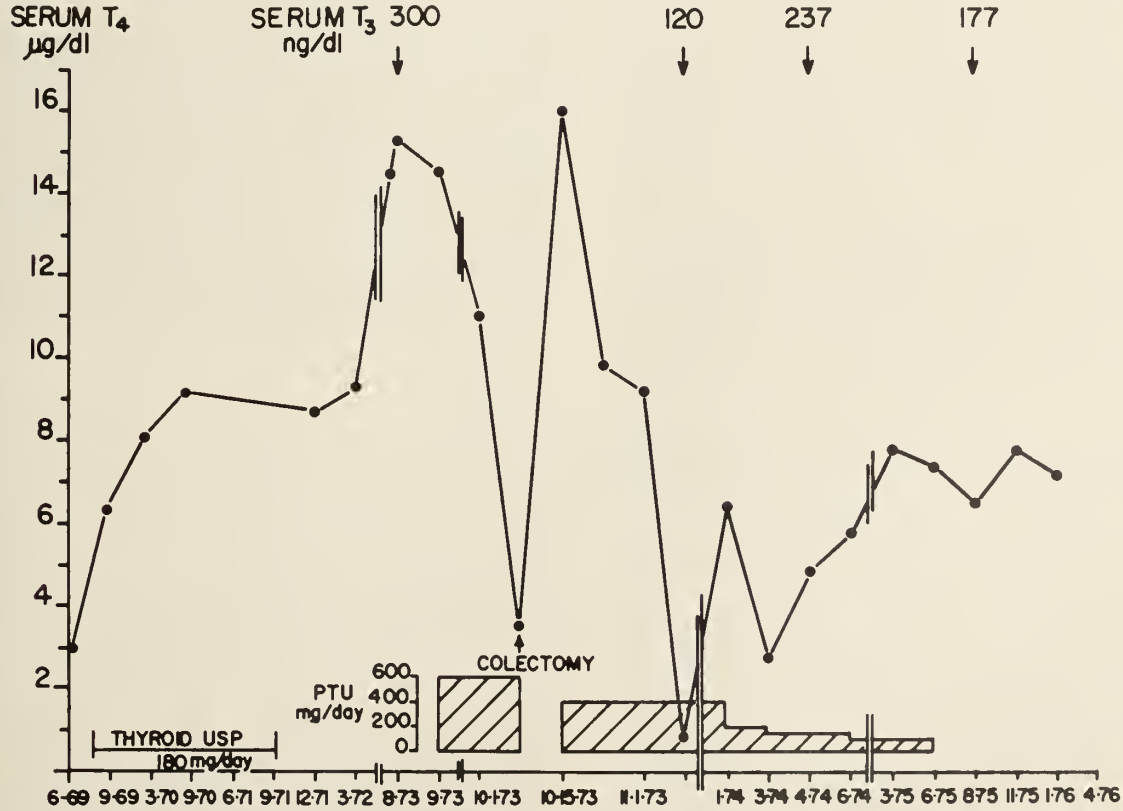

Figure 1.—Serum thyroxine (T_4) concentrations during the course of the patient's disease and therapy. Measurements of serum protein-bound iodine and T_4 iodine (before August 1973) are expressed as T_4, also. Serum triiodothyronine (T_3) levels at several times are shown at the top. PTU = propylthiouracil.

recurrent carcinoma was resected after two weeks of treatment with propranolol, propylthiouracil and iodine; the serum T_4 fell to 3.8 μg per dl at the time of operation. Iodine and propylthiouracil administration was stopped on the day of operation with a rebound of the serum thyroxine to the hyperthyroid range postoperatively. Propylthiouracil therapy was reinstituted and he became euthyroid. Bioassay of an extract of the colon tumor in mice showed no thyroid-stimulating activity; blood from a vein draining the tumor showed no TSH by radioimmunoassay.

After October 1973 the patient was maintained in a euthyroid condition with various doses of propylthiouracil (Figure 1). In December 1973, while the patient was still receiving propylthiouracil, a thyroid biopsy study was done.

Histologic slides (kindly reviewed by Dr. Lewis B. Woolner of the Mayo Clinic) showed small foci of oxyphilic epithelium and minor foci of lymphocytic infiltration, features compatible with mild Hashimoto thyroiditis. Other areas of thyroid parenchyma showed nonoxyphilic epithelium with some cuboidal or columnar cells and slight papillary infoldings. These findings suggested hyperthyroidism. During the next 18 months the hyperthyroidism was controlled with propylthiouracil therapy. In July 1974 the propylthiouracil was discontinued, and the patient has remained euthyroid through December 1977.

TABLE 2.—*Pituitary Function Tests*

	Insulin Tolerance Test (3/74)		
Time min	*Glucose mg/dl*	*Growth Hormone ng/ml*	*Cortisol μg/dl*
0	69	1.0	10.5
15	..	..	..
30	21	..	..
45	20	6.5	13.2
60	36	17	15.8
90	44	23	21.0
120	64	12	17.0

	Metyrapone Test (3 gram dose at 11 pm)	
	Cortisol μg/dl	*11-deoxycortisol μg/dl*
Baseline	8.7	<2
After metyrapone	3.2	11.5

Gonadal Function	
Luteinizing hormone	4 mIU/ml
Follicle stimulating hormone	6 mIU/ml
Serum testosterone	470 ng/dl

TABLE 3.—*Tests With Thyrotropin-releasing Hormone and Basal Serum T_4 and T_3 Levels*

Date	*Study*	*Basal TSH μU/ml*	*Peak TSH μU/ml*	*Serum T_4 μg/dl*	*Serum T_3 ng/dl*
1-74	TRH 500 μg IV	1.3	1.3	6.8	..
3-74	TRH 500 μg IV	1.2	6.1	2.8	..
3-75	TRH 500 μg IV	1.1	14.4	6.3	170
3-75	$N^{3\,1m}$-methyl-TRH 100 μg IV	1.4	21.6	6.1	170

T_4 = thyroxine
T_3 = triiodothyronine
TRH = thyrotropin-releasing hormone
IV = intravenously

Special Endocrine Studies

Studies of pituitary function were done to rule out hypothyroidism secondary to pituitary insufficiency. There was a normal increase in 11-deoxycortisol after metyrapone,[3] and normal cortisol and growth hormone responses to insulin-induced hypoglycemia (Table 2).[4,5] Serum luteinizing hormone, follicle-stimulating hormone and testosterone levels were also normal, as were findings on x-ray studies of the sella turcica.

The pituitary-thyroid axis was evaluated in 1974 and 1975 (Table 3). Initial testing with 500 μg of thyrotropin-releasing hormone (TRH) after four months of treatment of the hyperthyroidism produced no increment of TSH over the baseline. However, the serum prolactin increased from 4.2 ng per ml to 16.2 ng per ml. At this time the serum T_4 was normal and the dose of propylthiouracil had been recently decreased. In March 1974 a repeat TRH test produced a subnormal but measurable increase of TSH to 4.9 μU per ml; serum T_4 had fallen to 2.8 μg per dl and the dose of propylthiouracil was further reduced. Finally a third TRH stimulation in 1975 when he was euthyroid produced a maximum TSH increment of 14.4 μU per ml at 30 minutes, which was a normal response.[6]

Comment

Several possibilities merit consideration in trying to explain this patient's clinical course. Iodine-induced myxedema as the cause of the initial hypothyroidism was excluded by history and by the low serum PBI value initially. Subacute thyroiditis may cause transient hypothyroidism, but there was no history suggesting this entity. Furthermore, the few patients reported to progress from subacute thyroiditis to sustained hyperthyroidism have not gone through a hypothyroid phase. In a few patients with hypothyroidism and pituitary insufficiency, hyperthyroidism of Graves disease later developed.[7] In our patient there was no clinical evidence of pituitary insufficiency, and

specific evaluation of growth hormone, ACTH and gonadotropin secretion gave normal findings. The initial failure in this patient for TSH to be released after TRH stimulation is in accord with reports of patients euthyroid while receiving propylthiouracil or after treatment for hyperthyroidism in whom there was no response to TRH.[8,9] The duration of our patient's euthyroid status while receiving treatment may have been insufficient to allow recovery of normal pituitary responsiveness at the time of the first TRH test. However, by February 1975, while the patient was still receiving propylthiouracil, there was a normal response to both TRH and N^{3im}-methyl-TRH, a more potent analogue of TRH.[10] Serial studies of antithyroid antibodies in the patient showed a significant reduction in anticytoplasmic and anti-microsomal titers over several months in 1973 and 1974, although the thyrotropin-displacing activity of the serum was still present. The declining antibody titers and return of normal responsiveness to TRH suggested clinical remission of Graves disease.

Graves disease occurring in patients taking thyroid medication, as in our patient, has been reported in more than 100 cases.[11] In most of these cases the patients were euthyroid initially, but in a few a clinical diagnosis of hypothyroidism was the reason for treatment. In none was there a definitive laboratory documentation of the hypothyroidism and in no case could a causal relationship be proved between the thyroid medication and the Graves disease.

We found eight reported cases of hypothyroidism progressing to hyperthyroidism in which a diagnosis of autoimmune thyroiditis was established or postulated.[12-18] In only four cases, however, was the hypothyroidism well-documented.[12,13,17,18] The thyroid biopsy findings in our patient were consistent with Graves disease, with some features suggestive of Hashimoto thyroiditis. The antibodies present in our patient have been reported in both Hashimoto thyroiditis and Graves disease, which appear to be closely related primary immunological disorders. The exophthalmos in our patient is most consistent with Graves disease but has also been reported with Hashimoto disease.[19]

Most likely, the cause of our patient's hypothyroidism was autoimmune thyroiditis, with part of the gland subsequently regaining function and causing hyperthyroidism. The basis for this recovery must remain speculative. The possibility of the hyperthyroidism being due to a thyroid-stimulating substance from the adenocarcinoma of the colon was considered, but a thyroid stimulator could not be shown to be present. Current evidence suggests that autoantibody formation induced by a deficiency of suppressor T cells may be the cause of autoimmune thyroid disease.[20] The coincidence of repeated colonic malignancies in this patient suggests the possibility that a similar failure of immunologic control mechanisms may be involved in recurrent bowel cancer.

Summary

In a 58-year-old man Graves hyperthyroidism and recurrent adenocarcinoma of the colon developed four years after a diagnosis of spontaneous myxedema. Anticytoplasmic and antimicrosomal antithyroid antibodies and TSH-displacing activity were detected; bioassays of serum and of the malignant lesion of the colon for thyroid-stimulating activity were negative. Biopsy of the thyroid showed features compatible with mild Hashimoto thyroiditis. Pituitary function was normal. The patient has remained euthyroid after therapy with propylthiouracil. The development of Graves hyperthyroidism after a patient has become myxedematous from autoimmune chronic thyroiditis is rare. The coincidence of autoimmune Graves disease and recurrent colon cancer suggests the possibility that a similar failure of immunologic control mechanisms may play a causal role in both disorders.

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Cirrhosis Due to Hypervitaminosis A

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A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals.[1]

WILLIAM OSLER, 1891

We live in a health conscious society. Despite scientific evidence to the contrary,[2-4] many people believe the standard American diet to be nutritionally inadequate and, therefore, ingest a wide variety of supplemental vitamins. The purpose of this report is to point out the danger of hypervitaminosis A, and also to remind physicians that too much of this necessary vitamin can be a cause of chronic liver disease.

Report of a Case

A 72-year-old retired school teacher was first seen in October 1976 with complaint of ascites. The latter had been present for six months associated with at least a 40-pound weight gain. The patient said there had been no history of other symptoms, serious medical illness, liver disease, blood transfusions or alcohol abuse. For six to seven years he had taken vitamins A, B, C, D and E to "promote good health." The dose of vitamin A averaged 40,000 units per day. He took no other medication.

Physical examination showed the patient to be pleasant and alert. His skin was dry and red with telangiectasia over the face. Cheilosis was noted, but the intraoral examination showed no abnormalities. There was massive ascites, and pronounced peripheral edema.

Initial laboratory studies showed a mild pancytopenia with a hemoglobin value of 11.4 grams per dl, leukocyte count of 3,300 per cu mm and platelet count of 105,000 per cu mm. Findings on liver function tests were minimally abnormal with a total bilirubin value of 1.4 mg per dl; serum glutamic oxaloacetic transaminase, 80 IU per liter, and alkaline phosphatase, 150 IU per liter. Serum albumin was 3.1 grams per dl with a total protein of 5.4 grams per dl. Serum electrolytes, blood urea nitrogen, creatinine, iron, iron binding capacity, and thyroid function tests gave findings within normal limits. Prothrombin time was 40 percent. Serologic tests for hepatitis B surface antigen, alpha-fetoprotein and alpha-1-antitrypsin were negative, or within the normal range. A technetium 99m liver-spleen scan showed irregular uptake by a small liver, an enlarged spleen and shunting of activity to bone marrow consistent with cirrhosis. A diagnostic paracentesis gave findings consistent with a transudate, and ascitic fluid cytology and culture for tuberculosis were negative.

Administration of diuretics was started and over the next two months the patient lost 40 pounds of weight. The diagnosis was cirrhosis and portal hypertension secondary to hypervitaminosis A.

A serum vitamin A level drawn four months after stopping its ingestion was 39 μg per dl, within the normal range of 15 to 60.

Four months after his initial visit, the patient was feeling well, his skin was greatly improved and no ascites could be shown. Soon thereafter, however, he returned with complaint of weakness and black stools. The hemoglobin value had dropped to 6.7 grams per dl. Subsequent esophagogastroduodenoscopy showed bleeding esophageal varices, a normal stomach and proximal duodenum. Barium examination of the same areas confirmed the finding of varices.

Over the next two months there were three more episodes of acute bleeding from esophageal varices confirmed once again with endoscopic or

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roentgenographic methods. At no time were there signs of liver failure or hepatic encephalopathy.

In March 1977 a surgical operation was carried out and a side-to-side portacaval shunt established. The liver was grossly cirrhotic. Portal vein pressure dropped from 32 cm to 16 cm of water following the shunt procedure. Postoperative recovery was uncomplicated, and there have been no further signs of bleeding, ascites or encephalopathy.

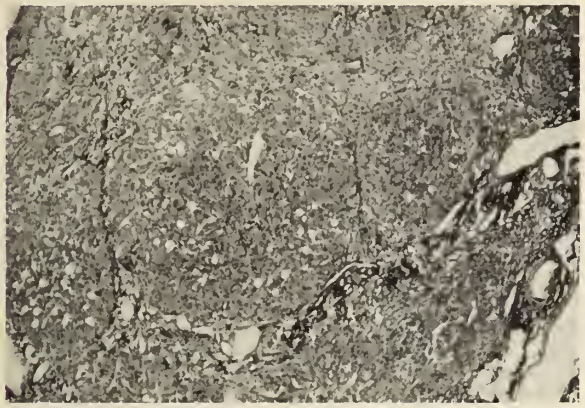

Figure 1.—Liver biopsy specimen showing nodule formation, fibrosis and dilated sinusoids. (Masson's trichrome stain, reduced from ×40).

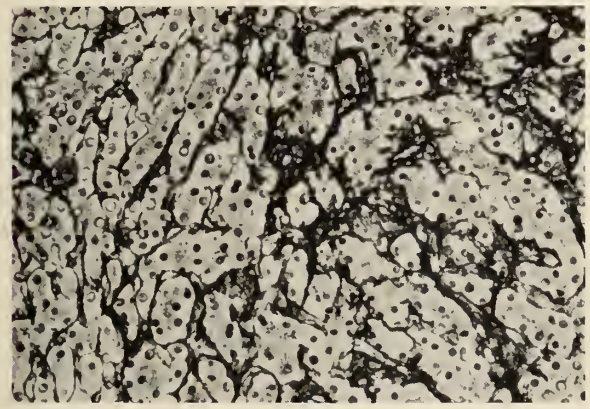

Figure 2.—Liver biopsy specimen showing pericellular fibrosis. (Silver reticulum stain, reduced from ×150).

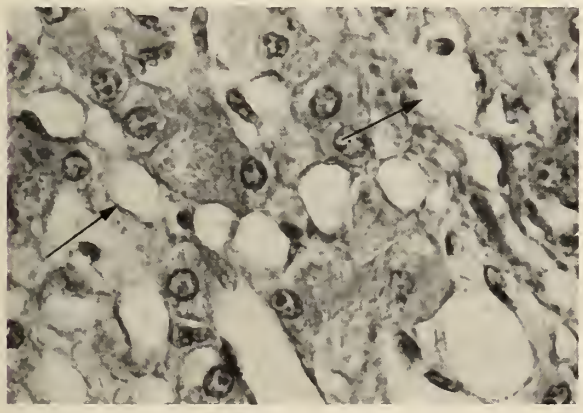

Figure 3.—Liver biopsy specimen showing lipocytes (arrows) and surrounding liver cells. (Hematoxylin and eosin stain, reduced from ×300).

Liver Histology

Liver biopsies were done by percutaneous needle several months before operation and at operation (see Figures 1-3). These showed nodule formation and fibrosis consistent with cirrhosis, sinusoidal dilatation, sclerosis of central veins, and lipocytes within sinusoids and fibrous septae. These findings are consistent with vitamin A liver toxicity.[5]

Discussion

Vitamins are not synthesized in the body and, therefore, must be taken in from an exogenous source.[4] It is generally believed that an average person receives the recommended daily dose of vitamin A (5,000 IU) from a well-balanced diet.[2-4] Once absorbed, this vitamin is stored in the liver as its ester, and can later be converted to the biologically active form, and then released into the blood.[4,6]

Muenter and co-workers[7] reviewed 17 cases of chronic vitamin A toxicity and found a daily intake of 41,000 to 600,000 units over periods ranging from a few months to nine years. Signs and symptoms included weakness, hair loss, rash, headache, muscle stiffness, bone pain, hepatosplenomegaly and papilledema. There are several reports of serious liver damage secondary to hypervitaminosis A with eventual cirrhosis and its serious sequelae.[5-7]

The exact pathogenesis of vitamin A-induced liver damage is not clear. There is evidence to suggest that excessive vitamin A within the liver leads to fibrosis, sclerosis of central veins and obliteration of sinusoidal spaces with subsequent portal hypertension and ascites.[5]

Our patient had taken at least 40,000 units of vitamin A for more than six years. His physical appearance, rash, cheilosis, laboratory test findings, liver biopsy material and subsequent course are all consistent with vitamin A toxicity leading to cirrhosis, ascites and eventually esophageal varices. Although the serum vitamin A level was normal, the specimen was drawn some four months after the vitamin ingestion was stopped;

moreover, serum levels may remain normal until vitamin A storage capacity in the liver is exhausted.[7]

All patients should be questioned about vitamin intake. Those with abnormal liver function should be carefully screened for hypervitaminosis A.

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Phenytoin Overdose Kinetics

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THE USE OF prescription medications in attempted suicides is a major medical and social problem. Therapeutic difficulties may arise from the fact that the pharmacology of the drugs ingested often differs greatly when comparing therapeutic doses versus overdoses. In addition, massive amounts of drug may overwhelm clearance mechanisms. The purpose of this paper, then, is to emphasize this difference in pharmacokinetics with phenytoin overdose as it influences management.

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Report of a Case

A 54-year-old man was admitted to the detoxification ward at Los Angeles County-University of Southern California Medical Center on January 22, 1976. Upon admission he appeared intoxicated and was described as confused and incoherent. He was crying loudly and passive restraints were required. Vital signs were reported as a pulse of 104 beats per minute, respiratory rate of 20 breaths per minute, temperature of 37.2°C (99°F) (rectally) and blood pressure of 150/100 mm of mercury. His chest was clear to auscultation. There were no focal findings on neurologic examination and there was no evidence of head trauma. The cardiac rhythm was regular. The toxicology report indicated a phenytoin level of 6.9 mg per dl (with therapeutic levels reported as 1 to 2 mg per dl), a phenobarbital level of 6.3 mg per dl (with therapeutic levels reported as 2 to 4 mg per dl) and a negative ethanol level.

Past medical history was obtained from a previous admission. The patient had a history of epilepsy for 18 years following trauma, a history of gastrectomy and previous heavy drinking. Anticonvulsant therapy was begun in 1969 with phenytoin, 100 mg orally three times a day, and phenobarbital, 30 mg orally three times a day.

Hospital Course

On the day of admission the patient was very confused. Body temperature rose to 40°C (104°F). Phenytoin and phenobarbital levels were 6.9 mg per dl and 6.3 mg per dl, respectively (see Table 1). On the second hospital day, he was still lethargic, with slurred speech. He moved all extremities nonpurposefully and remained very agitated. The temperature had fallen to 38.3°C (101°F) without antibiotic or antipyretic drug therapy. On examination the patient had gross nystagmus and ataxia. He was extremely labile emotionally, with episodes of crying and moaning. In addition he was disoriented to person, place and time. Restraints were required for three days. On the third day, the patient remained disoriented and in an apparent psychotic state. He continued to groan loudly and there were periodic bursts of crying. His speech was slurred and unintelligible. The following day serum levels were obtained and indicated a phenytoin level of 6.7 mg per dl and a phenobarbital level of 5.0 mg per dl. Serum level determinations were repeated on the next day, the fifth hospital day, and levels were re-

duced to 5.3 mg per dl for phenytoin and 3.3 mg per dl for phenobarbital. Since the phenobarbital level was in the therapeutic range, administration of the drug was reinstituted at 30 mg given intramuscularly three times daily. The patient's mental status remained unchanged until the sixth day after admission, when he was able to communicate. He was oriented to person and place but continued to be notably agitated. The presence of nystagmus and ataxia persisted but to a lesser degree than on admission. At this time he admitted to taking three phenytoin capsules three times per day and also taking three times the prescribed amount of phenobarbital.

On the sixth day, the reported phenytoin and phenobarbital serum levels were 4.8 mg per dl and 3.4 mg per dl, respectively. At this time the patient was still drowsy but no longer very agitated. On the ninth day, nystagmus was no longer present but ataxia was observed. The phenytoin level was 4 mg per dl. On the 14th day, the phenytoin level was 0.4 mg per dl and a maintenance dose of 300 mg per day was started. At this time the patient continued to be slightly unstable while walking, possibly due to chronic alcohol-induced cerebellar disease.

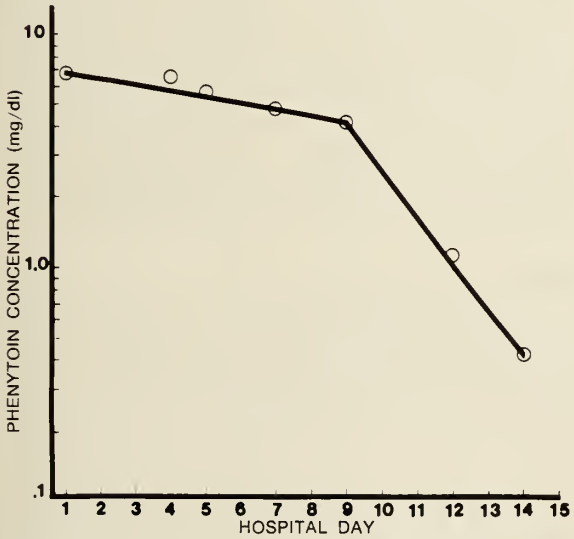

Figure 1.—Plot of the log of the serum phenytoin concentration versus time in days.

Treatment consisted of supportive care until the patient became less confused and agitated. No medications were administered during the acute psychotic phase. Hard restraints were employed to prevent injury to the patient. Hydration was maintained by intravenous administration of fluids. After 15 days in hospital, the patient was discharged and continued on a regimen of anticonvulsant medications.

Discussion

Our premise is that an understanding of the pharmacokinetics of phenytoin will influence therapeutic decisions in an overdose situation. The plasma half-life of phenytoin has been shown to be dose dependent in man.[1] In other words, the time required for the plasma level to halve itself increases as the concentration of the drug increases. An explanation for the nonexponential decline of phenytoin is that the biotransformation mechanism approaches saturation at higher plasma levels.[2] Therefore, the disappearance of the drug is not a simple exponential process and does not follow apparent first order kinetics. According to Atkinson and Shaw, the elimination follows a fixed rate at high plasma concentrations or zero order kinetics (as seen with ethanol).[3] This would explain the persistence of symptoms for several days at high plasma concentrations of the drug. The half-life of phenytoin for healthy adults averages 22(±9) hours (range 7 to 42 hours).[1] In our patient the plasma half-life was 9.6 days for that period of time when the plasma level fell from 6.9 mg per dl to 4.3 mg per dl (see Figure 1). During this ten-day interval, phenytoin elimination is best described as showing Michaelis-Menton kinetics. However, once the phenytoin level fell below 4.0 mg per dl (on the ninth hospital day) various metabolic pathways were no longer as saturated. After this time, the phenytoin half-life was 30 hours and was con-

TABLE 1.—*Symptoms of Phenytoin Toxicity in Conjunction With Phenytoin and Phenobarbital Serum Levels*

	HOSPITAL DAY															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Nystagmus	4+	(*)	→	3+	→	→	2+	→	→	→	1+	→	→	→	→	→
Confusion	4+	→	→	3+	2+	→	1+	→	→	→	→	→	→	→	→	→
Ataxia	4+	→	→	→	→	3+	→	→	2+	→	→	→	→	→	→	1+
Serum phenytoin (mg/dl)	6.9			6.7	5.3	4.8			4.2		1.2		0.4			
Serum phenobarbital (mg/dl)	6.3			5.0	3.3	3.4			3.1		3.0					

*This is an attempt to quantitate subjective signs and symptoms: 4 = severe, 3 = moderate, 2 = mild, 1 = minimal.

sistent with a faster rate of decline. The patient exhibited the classical signs of phenytoin dose dependent side effects (nystagmus, ataxia and confusion) for nearly ten days after entering the hospital. Were the elimination rate unchanged in the overdose situation, the patient would have been asymptomatic after three days. Therefore, when a patient enters the hospital after taking an overdose of phenytoin, toxicity may persist for many days until the metabolic rate of elimination increases and phenytoin levels fall below the toxic range.

The possibility of delayed absorption cannot be excluded since three days passed between the first two determinations of phenytoin levels. In fact, this has previously been described.[4] In our patient there could have been a continued rise in phenytoin levels secondary to persistent absorption during the second and third hospital days.

Although there are insufficient data to determine a representative lethal drug concentration, Laubscher reported a fatal phenytoin ingestion associated with a peak plasma level of 9.4 mg per dl.[5] In general, phenytoin levels in excess of 10 mg per dl may require measures beyond supportive care. If the patient cannot tolerate toxic phenytoin concentrations, other measures should be undertaken to increase the elimination rate. Dialysis is one means and has been advocated by some,[6-8] but found to be relatively ineffective by others.[9]

In conclusion, the successful management of a patient with phenytoin overdose is enhanced by good clinical judgment, successive plasma drug level determinations and an appreciation of phenytoin kinetics.

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Ventricular Tachycardia in a Young Adult With an Apical Aneurysm

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FINDING THE CAUSE of frequent ventricular extrasystoles in a young, presumably healthy patient is difficult. Often, no pathologic condition can be found to account for the arrhythmia despite extensive cardiac evaluation. This paper reports the unusual finding of frequent ventricular extrasystoles and ventricular tachycardia in a young adult with an apical cardiac aneurysm. The cause of the aneurysm was felt to be infection with the parasite Trypanosoma cruzi (Chagas disease). Surgical removal of the left ventricular aneurysm ablated the arrhythmia. Surgical removal of the apical aneurysm for control of arrhythmia has not previously been reported in Chagas disease.

Report of a Case

A 23-year-old woman from El Salvador was referred to the Los Angeles County-University of Southern California Medical Center for investigation of an abnormal heart rhythm. The patient had no serious illnesses and had had a normal baby two years before admission. There was no history of heart disease, chest trauma, rheumatic fever, hypertension or diabetes mellitus. She had lived in the United States for three years.

On examination, the patient appeared well. Her blood pressure was 120/70 mm of mercury, pulse 60 and irregular and respirations normal. The lungs were clear, and there was no neck vein distention. The heart was not enlarged, and the

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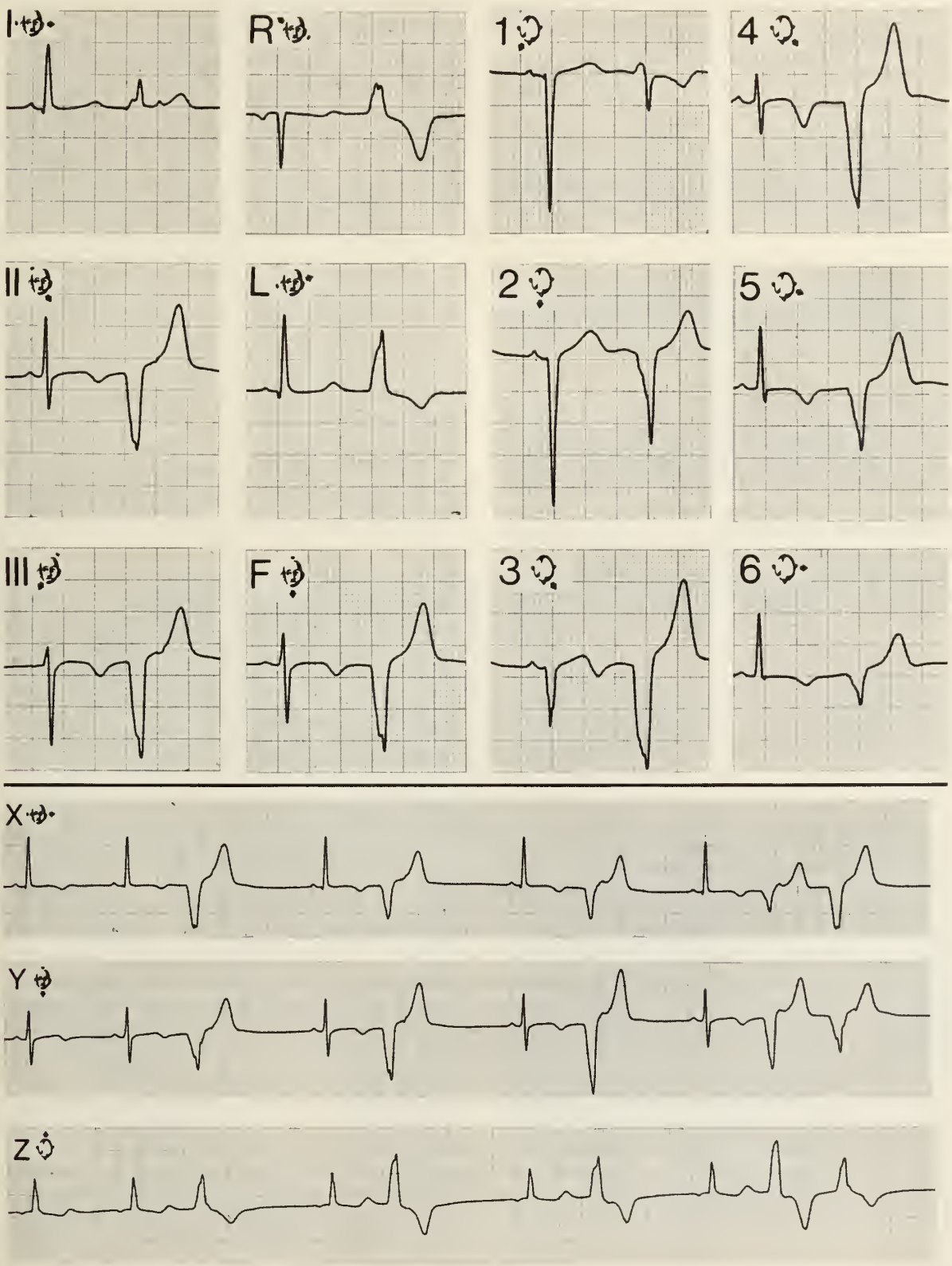

Figure 1.—A, 12-lead electrocardiogram and **B,** XYZ rhythm strip at time of cardiac catheterization.

apical impulse was normal. The first and second heart sounds were normal. A grade II/VI systolic ejection murmur was heard at the second intercostal space; it did not radiate.

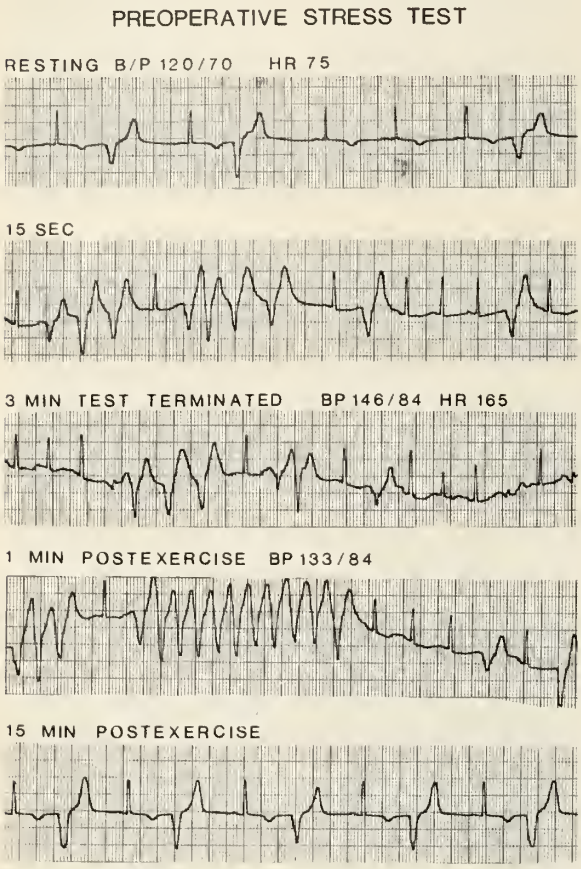

Figure 2.—Bruce protocol maximal treadmill stress test with resultant ventricular tachycardia.

Figure 3.—Cineangiographic projection of left ventricle in the right anterior oblique position. The left ventricular apical aneurysm is noted.

An x-ray film of the chest, complete blood count and differential, erythrocyte sedimentation rate, biochemistry profile, and studies of cardiac enzymes showed no abnormalities. An electrocardiogram (Figure IA) showed poor progression of the R wave in V_1 through V_3, and inverted T-waves in V_3 through V_6. Frequent ventricular extrasystoles of left ventricular origin, with slight coupling variation, were noted. A phonocardiogram recorded normal heart sounds and the murmur, as previously described. No gallop sounds were noted. An echocardiogram showed normal-sized chambers and normal aortic and mitral valve motion. Paradoxical motion of the interventricular septum was noted below the level of the mitral leaflets. An exercise stress test was done using a standard Bruce protocol.[1] The patient had ventricular bigeminy at rest, and after three minutes (stage 2) of exercise, ventricular tachycardia developed (Figure 2). The test was terminated; the tachycardia stopped spontaneously. One minute after exercise the patient had another short episode of ventricular tachycardia. During the episode of ventricular tachycardia (240 per minute), the patient was asymptomatic; the blood pressure was 110/80 mm of mercury.

Because of the abnormal findings on the stress test, electrocardiogram and echocardiogram and the relative absence of abnormal physical findings, cardiac catheterization was indicated to further assess the patient's problem. Pressure measurements were normal (left ventricular end-diastolic pressure, 10 mm of mercury; pulmonary artery pressure, 30/10 mm of mercury with a mean of 20 mm of mercury), and no intracardiac shunts were detected. Cineangiograms showed normal right and left coronary arteries. An aneurysmal outpouching of the apex of the left ventricle was clearly visualized, with an estimated volume of 9 cu cm (Figure 3). Cardiac catheterization was complicated by the development of ventricular tachycardia during initial hemodynamic measurements; no contrast agent had been given. The systolic pressure was 98 mm of mercury during the ventricular tachycardia.

The rightward, superior and posterior direction of the ventricular premature beats illustrated with the Frank lead system (Figure 1B) localized the origin of the ventricular premature beats to the area of the left ventricular apex.[2] The left ventricular aneurysm was therefore considered to be the source of the arrhythmia. Medical management with xylocaine, digoxin, procainamide and quini-

dine did not effectively control the frequent episodes of ventricular arrhythmias and prompted surgical excision of the ventricular aneurysm.

At operation, a thin aneurysm measuring 4 cm at the base and 3 cm in length was identified at the left ventricular apex (Figure 4A). There was no defect in the pericardium, and no adhesions were found in the pericardial sac. The surface of the aneurysm was smooth, and no discoloration was noted. Paradoxical motion was noted along the aneurysm wall with systole. The remainder of the cardiac muscle appeared normal. Using cardiopulmonary bypass, the aneurysm was completely excised and the defect closed with interrupted sutures over Teflon® felt strips. No mural thrombus was noted in either the left ventricle or the aneurysm. The postoperative course was uneventful. The patient was discharged on the tenth day without antiarrhythmic therapy.

The excised aneurysm measured 2.5 cm in diameter and 2.5 cm in length; the wall was 1 to 3 mm thick. The surface was smooth, and no discoloration was noted. Microscopic examination (Figure 4B) showed severely disorganized myocardium, with prominent fibrous scarring and intense lymphocytic and eosinophilic infiltrates. Myocardial muscle layers were not distinct. A titer for the indirect hemagglutination reaction for Trypanosoma cruzi was present, 1:128, as determined by the Center for Disease Control in Atlanta.[3]

During a two-year follow-up period, there has been no evidence of recurrence of ventricular arrhythmias, and repeat stress testing has shown no ventricular ectopic beats.

Discussion

In some areas of South and Central America, infection with the protozoal parasite Trypanosoma cruzi is a common cause of cardiomyopathy. World Health Organization sources have estimated that approximately 7 million people are infected with the parasite.[4] Of these, 50 percent may have signs and symptoms of cardiomyopathy. Chagas cardiomyopathy in the United States is, however, very unusual. Infection with the parasite

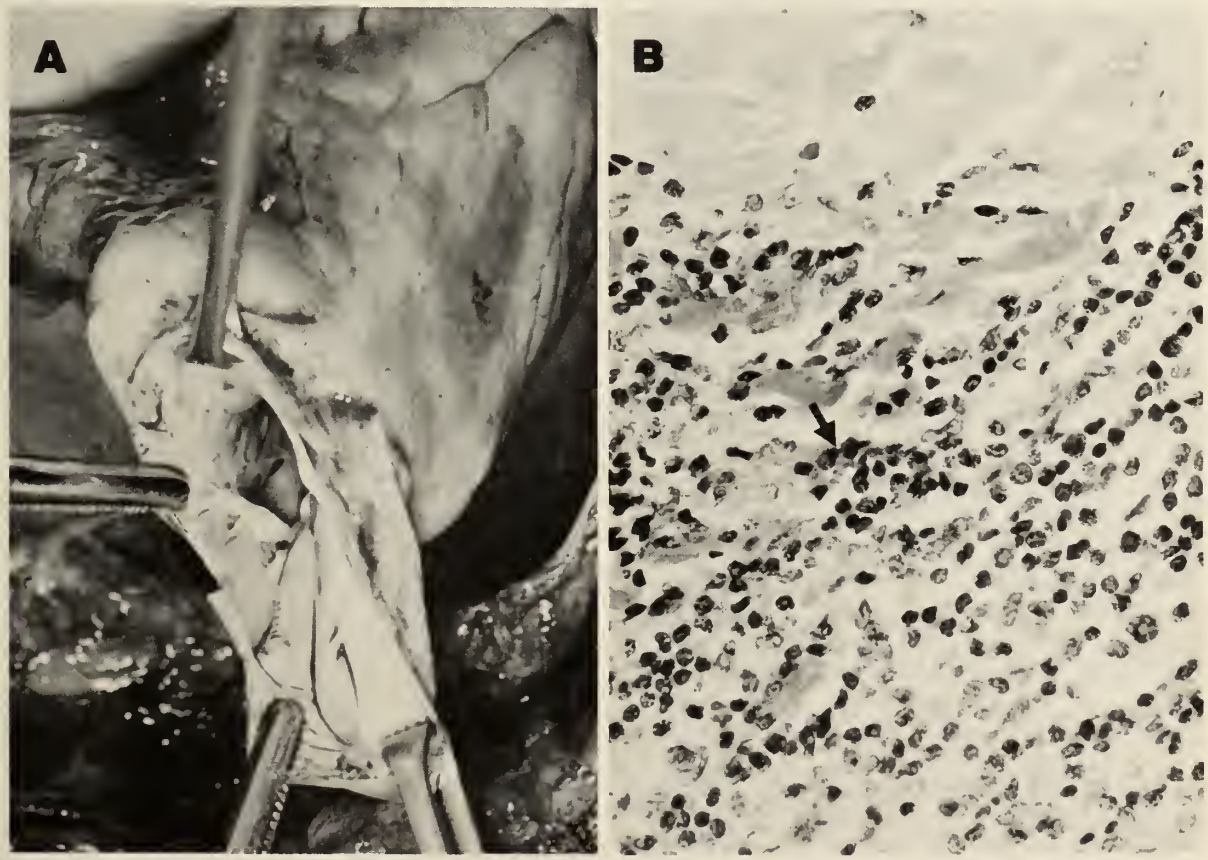

Figure 4.—**A**, Photograph taken at surgical operation of left ventricular aneurysm, **B**, Microscopic section of the resected aneurysm (x500), noting destruction of musculature, eosinophils **(arrow)** and histiocytes.

in the continental United States has been reported a few times, most often as a result of accidental laboratory inoculation.[5,6] As intercontinental travel to and from Central and South America increases, it is necessary to consider unusual causes for cardiomyopathy and the genesis of arrhythmias. This case report is an example of the presentation of Chagas cardiomyopathy at a large metropolitan United States hospital.

Infection with Trypanosoma cruzi is via cutaneous contamination of a wound by a family of blood-sucking triatomid bugs, most commonly the reduvid bug.[7-12] The protozoa are inhabitants of the insect's digestive tract, and passive transfer of fecal material to skin or mucous membranes takes place after the insect feeds. If the palpebral area is the portal of entry, unilateral palpebral edema or Romaña sign may be present. More often, the portal of entry is a bite on the arm or leg, and usually goes unnoticed. An acute phase of the disease is sometimes recognized by fever, malaise, myalgia and other nonspecific constitutional symptoms and signs. During this phase, the parasite may be found in the free-swimming trypanosomal form in the blood stream. Multiplication takes place in the cells of the reticuloendothelial system, muscle or nerve sheaths. Cardiac symptoms during the acute phase are the result of a toxic myocarditis. Slight, reversible cardiomegaly to severe, lethal congestive heart failure may be present. Mortality estimates during the acute phase range from 2 to 10 percent.[8,10,12] Since the initial infection frequently takes place in early childhood, the acute phase may pass unnoticed to a subacute, latent stage. After a period of 10 to 30 years, a clinically recognizable, chronic phase of the disease is seen. The major organ involvement during the chronic stage is the heart and the neurovascular bundles of the gastrointestinal tract. Myocardial destruction is due to multiplication of the protozoa within the myocardium and resultant inflammatory or autoimmune destruction of muscle cells. During the chronic stage, diagnosis is made by clinical suspicion, usually based on geographical location and serological testing. Organisms are not seen in the blood stream, and are only recognized in tissue specimens after careful study.

Cardiomyopathy is one end result of infection with Trypanosoma cruzi. Because there is a latent period, the transition from an asymptomatic stage to the onset of heart disease is difficult to define. Electrocardiographic abnormalities, including bundle-branch blocks, atrioventricular block, ventricular extrasystoles and nonspecific QRS abnormalities are often the first recognizable signs of cardiac involvement.[8,11,13] Death, often sudden, is due to congestive heart failure, atrioventricular block, arrhythmia or embolic phenomena.

Although most patients with Chagas cardiomyopathy have diffuse enlargement of all chambers, a localized apical ventricular aneurysm is characteristic of the disease.[8,10-12,14-16] These thinned, bulging aneurysms are at the apex of either the right or left ventricle, and have been seen in up to 70 percent of cases studied at autopsy.[15,17] The aneurysms have only been reported in the chronic phase of the disease in man, but have been experimentally produced in dogs after acute infection with T. cruzi.[18] Anterior ST segment elevation is common in patients with the apical abnormality; it is also seen in animal studies. Histologically, the aneurysm is characterized by myocytolysis, fibrosis, and an intense lymphohistocytic and eosinophilic invasion. Thrombosis may be present within the aneurysm. The mechanism of aneurysm formation is not known. Theories[9,10,12,14,19,20] include immunoallergic inflammatory destruction of musculature, hypoxia associated with lesions in the coronary vessels, mechanical unwinding of muscle bundles causing herniation of the endocardium, and neurotoxic destruction. None satisfactorily explains the presence of the ventricular aneurysm. Clinical consequences of the aneurysm include arrhythmias, especially ventricular extrasystoles with episodes of ventricular tachycardia; embolic phenomena; and aneurysmal rupture.[17] Findings on limited catheterization studies have suggested that the apical aneurysm, by itself, is not enough to account for global congestive symptoms.[15,21]

Ventricular arrhythmias are a common cause of death in Chagas cardiomyopathy. Ventricular extrasystoles and ventricular tachycardia are associated with an increased incidence of sudden death. In Laranga's extensive study of 683 patients,[8] ventricular extrasystoles were recognized in 45 percent and ventricular tachycardia in 2 percent. In the fatal group of 200 patients, 69 percent had ventricular extrasystoles. In 21 cases in which autopsies were done, there were apical aneurysms in six. All had had ventricular extrasystoles.

These clinical features described in the literature suggest that the findings noted in our patient represent Chagas heart disease. There were no

clinical symptoms or signs of congestive heart failure. Cardiac catheterization showed normal pressures and pulse contours. Electrocardiograms suggested anterior fibrosis or aneurysm formation, and echocardiograms confirmed abnormal septal motion. The pathologic findings appeared to be limited to the apex of the left ventricle, although a more diffuse process is possible. Sclerosis and intimal changes in the coronary vessels have been proposed as a cause of the apical aneurysm.[14,16] Coronary angiography, however, has not been systematically studied in a large number of these patients. Accepting the intrinsic limitations of coronary arteriography, it is interesting to note that there were no abnormalities in our patient. The arrhythmia was, however, potentially life-threatening, and was felt to be due to the localized apical disease. Surgical removal of the aneurysm eliminated the ventricular extrasystoles and episodes of ventricular tachycardia. Although this patient has had a dramatic clinical response to surgical removal of the ventricular aneurysm, the long-term prognosis is unknown. Two years after operation the patient is free of arrhythmias and there are no other manifestations of Chagas disease, such as impaired ventricular function, conduction defects or congestive heart failure.

Summary

Although the lack of definitive treatment available for Chagas heart disease needs to be emphasized, this case illustrates that surgical removal of localized disease may alleviate a potentially life-threatening source of arrhythmia and should be considered a mode of therapy. Awareness of the entity of Chagas cardiomyopathy is necessary, as illustrated by this report. A rational approach utilizing all available modalities in the evaluation of patients with ventricular arrhythmias and the potential for surgical treatment of ventricular arrhythmias when due to localized myocardial disease are emphasized.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Donald Kennedy Replies

To the Editor: I was both dismayed and disappointed by Dr. Ungerleider's letter, "The 11th Myth" (Correspondence, February issue), in which he launches a loosely-organized rhetorical barrage against the Food and Drug Administration's policies on controlled substances. Of all people, he should understand that the problems facing regulatory agencies in dealing with controlled substances, specifically marijuana, are neither readily solved nor subject to the control of a single federal agency. I would have thought that his service on the National Commission on Marijuana and Drug Abuse, not to mention his frequent contact with the agency on just these matters, would have kept him on firmer ground.

To begin with, he should recognize that the Food and Drug Administration (FDA) is hardly the first jurisdiction to develop a concern about public safety in connection with amphetamines. The question of amphetamine abuse has been raised time and again; the state of Maryland made it unethical to prescribe the drug for obesity more than four years ago, and in Wisconsin similar action was taken in 1977. Canada has done likewise. Can it be that each of these governments has independently developed the same style of data "massage" which Dr. Ungerleider attributes to FDA? Our actions are not, as Dr. Ungerleider states, "an attempt to abolish [amphetamine] use in obesity, depression and other conditions." Instead, they are designed to call the attention of practitioners to a serious problem, and to bring the labeling of amphetamines into line with a need to protect the public health.

As to the bizarre events surrounding Dr. Arnold Mandell's brief involvement with the National Football League, they are obviously beyond the point here—which is perhaps fortunate, since they are also beyond my comprehension. If the Board of Quality Assurance in California placed heavy emphasis on the *Physicians's Desk Reference* in disqualifying Mandell, that was their choice; we didn't help at all. The statement that not following the label can leave one "open to medical malpractice" is equally irrelevant to the issue. As I said in my article (Ten medical myths about FDA. West J Med 127:529-534, Dec. 1977), "the important consideration is whether departure from approved indications is documented *by a legitimate scientific rationale for such use.*" (Italics added.) That determination is in the hands of 50 legal jurisdictions, and out of FDA's.

At the amphetamine hearings held in December 1977, the presiding official—not identified by Dr. Ungerleider in his letter—was J. Richard Crout, MD, Director, Bureau of Drugs. A review of the transcript fails to reveal any statement by Dr. Crout about the California case that remotely fits Dr. Ungerleider's description: " . . . that the FDA *made* regulations, but was not responsible for what happened to them thereafter (that is, we just built an atomic bomb, but it is not our responsibility who drops it)." The transcript does indicate a view that Dr. Ungerleider's testimony raised a number of complaints, some within FDA's province but others involving state laws and litigation practices over which FDA has no control. An offer was made to meet with Dr. Ungerleider to help sort out these complex issues more carefully.

Dr. Ungerleider describes as "bureaucratic bumbling" the "overlapping" of two FDA Drug Abuse Advisory Committees. One of these committees had concerned itself with the basic interests of health care practitioners in the decision whether to classify drugs as "controlled." The second committee had a different objective; it evaluated proposed research in relation to established efforts. The White House did indeed request the

formation of the Public Health Service (NIH) committee to which Dr. Ungerleider refers. It was actually created, however, not because of FDA problems, but as an interagency device to stimulate research in areas where controlled drugs may be useful—as in such conditions as glaucoma, chronic pain and nausea, and vomiting secondary to cancer chemotherapy.

As Dr. Ungerleider must realize, at least three separate federal agencies are involved in drug abuse issues: the Drug Enforcement Agency (DEA), the National Institute for Drug Abuse (NIDA) and the Food and Drug Administration. Each organization has a distinctive function *mandated by Congress*. We work together, as well as we know how, to reduce bureaucratic problems in a complex regulatory environment not of our own design.

Dr. Ungerleider also cites FDA's alleged refusal to allow women of child-bearing potential to participate in the testing of marijuana for cancer chemotherapy patients. It is difficult to know what he is complaining about; as he knows perfectly well, his own comments on that policy led to FDA's revision of it. One of the points in my article was that FDA is working with health professionals to solve problems. He raised one, and we solved it together. Am I missing something?

Finally, although it is true that marijuana remains in Schedule I of the Controlled Substances Act, this classification is now under medical and scientific review; it will be discussed at the next meeting of the Controlled Substances Advisory Committee. To state that this position is "absurd," and that it continues to "bode ill for the research and treatment communities" is hyperbolic. The claim that research on drugs and their investigational use in treatment has been delayed when drugs are in Schedule I is by no means unclouded. Other factors—lack of funds, lack of good scientific ideas—are also involved.

Let me reiterate the promise that FDA's hopes for communication with health professionals are genuine, and that we are prepared to confess some sins—even "bumbling"—as our part of that process. But I scarcely know how to deal with the kind of hostility displayed in Dr. Ungerleider's letter. It goes so far beyond the specific arguments he cites—even if one were to grant their truth—that I think it must relate to another agenda entirely.

DONALD KENNEDY
Commissioner of Food and Drugs
Department of Health, Education, and Welfare
Rockville, Maryland

The Abortion Crisis—A Countervailing View

To THE EDITOR: Considering the fact that Dr. DeLee's opinion on the abortion issue (Correspondence, December 1977) is not the only one extant within the profession, publication of the following countervailing views would seem to be in order—if your readers are to get the full picture and a more balanced perspective on this matter.

The burden of DeLee's argument is that the children who might be born to Medicaid recipients (at least the great majority of them) are destined to become either criminals or pregnant (probably both equally bad in his book), and will therefore cost taxpayers an untold amount of money. This is a prime example of what Allen Chase calls scientific racism; that is, the belief that poverty and its attendant problems are heritable defects that can be eliminated only by wiping out the poor. (See his new book *The Legacy of Malthus,* which is well worth reading.)

On the contrary, proper prenatal care, nutrition, education, and the like, can, in fact, make poor children as "socially desirable" as yours or mine. These programs will also cost a lot of money, but the investment will be well worth it, and this solution is far more in keeping with the announced purposes of the medical profession than genocide against the poor.

In this context, it is important to note that no one questions the existence of the social and economic problems to which DeLee alludes. But many of us still do not accept the concept of expediency; that is, that the ends justify the means. Nor do we accept utilitarianism, that the determining consideration of right conduct should be the *usefulness* of its consequences.

In another of his arguments, DeLee again puts forth the old canard to the effect that refusing to perform an abortion amounts to "forcing" a woman to bear an unwanted child. Unless pro-abortionists are expecting us to buy the incredible proposition that the million plus abortions done annually are the result of rape, we assume that the choice about bearing an "unwanted" child can be (and should be) made before the woman says "yes" to intercourse.

In this context, we are being asked, it seems, to believe that women who say "yes" to intercourse can't control themselves, don't know their own minds or don't know the implications of their

decisions; that is, that they have no real choice. But at the same time, we are being asked (by the same proabortionists) to believe the contrary proposition: that the very same women do have a real and meaningful choice when they say "yes" to abortion.

Why are the same women so competent, astute and omniscient in one situation, but so incompetent, inept and ignorant in the other? It would appear that the proabortionists can't have it both ways. Such special pleading just won't wash.

Regarding Dr. DeLee's statement "the rights and opinions of others deserve respect, too"; I would concur in it, and give it even greater emphasis by reminding Dr. DeLee, and other like-minded persons, that this also applies to prolife people (who are also full-fledged citizens and taxpayers)—and to their consciences.

After all, DeLee is not merely addressing himself to the question of whether or not someone or anyone should be *legally* (as opposed to *economically*) impeded in seeking an abortion. We are dealing here, primarily, with the question of whether or not those who vehemently disagree with the "moral" perspective expressed by DeLee shall be *forced* (by the police power of the state) to contribute with their tax dollars to the implementation of institutionalized crimes against humanity, and thus be *forced* to become accessories before and after the fact—against their loud and repeated conscientious objections.

Finally, let me just observe that it hardly redounds to the credit of organized medicine, which has continually paid loud lip service to the concept of "freedom of conscience" (especially in the area of abortion) to be now supporting the ongoing assault, by those such as DeLee, against the consciences of what is, admittedly, now a defenseless minority of physicians within medicine's own ranks.

Although such attitudes about the "freedom to conscientiously object" are now held apparently only by a minority within our profession, fortunately such views are still held by the majority of the larger society (if we can believe recent polls). Some of us find hope and comfort in the fact that this larger majority is now prepared to avail itself of established legal remedies in redressing its grievances against the secularistic elite (mainly in the media and academia), which has persisted in forcing *its* "moral" views on the larger society.

JAMES H. FORD, MD
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Member, Committee on Evolving Trends in Society Affecting Life
California Medical Association

The Science and the Art

To the Editor: I like your editorial in the February issue ("Trends in the Science and the Art"). I too am worried about the concept that every medication must be proven scientifically to be effective. Not only may this take a long period of time, but it removes from our armamentarium one of the most universal and powerful drugs we have, namely the placebo. If there is some evidence that a drug is effective for a certain condition, what is the harm if the Art of Medicine condones its use, even though we may suspect that it is only a placebo effect. A dash of spice does not improve the nutritional quality of food, and a dash of Art (call it magic, if you wish) may not cure the patient. But, it will improve his ability to tolerate illness until the body's intrinsic healing mechanisms are successful.

ALBERT E. WARRENS, MD
Chico, California

Refer to: Comfort A: Geriatrics—The missing discipline? (Commentary). West J Med 128:257-259, Mar 1978

Commentary

Geriatrics — The Missing Discipline?

ALEX COMFORT, MB, BCh, DSc, *Santa Barbara, California*

IT WAS AN AMERICAN, Nascher, who first applied the term geriatrics to the medicine of old age. From the pioneer work of Warren, Sheldon and Ferguson Anderson in Britain and Doberauer in Austria, European geriatric medicine has undergone a remarkable florescence. By a curious accident of medical history, it is now the one major medical resource unavailable to the generality of American patients. Pockets of geriatric training exist in the Veterans Administration and some of the great Jewish hospitals, where the old are a traditional concern, but its absence from medical school instruction nationwide is one of the features of American medical education that most surprises an immigrant European doctor, if only on grounds of demography.

Geriatrics in Europe exists as a specialty, with ten university chairs in Britain alone. Some such infrastructure is needed to maintain consultation and research. At the same time, geriatrics is seen as part of the equipment of general internists and primary care physicians who are the linchpins of European health care delivery; a recent planning report in Britain recommends that general physicians with a special interest in geriatrics, rather than specialists who see only the old, should take charge of the geriatric unit in every major hospital, to avoid compartmentalization of medicine.[1] It may be this avoidance of one more subdivision which American deans of medical schools have in mind when they say that geriatrics is not a specialty. If, however, they mean that it does not have to be learned, and that symptomatology, dosages, drug responses and therapeutic options learned from standard internal medicine, which is in fact the medicine of young and middle-aged adults, can be summarily applied to persons over the age of 65 or 70, they are quite simply wrong. It used to be said that "any good doctor can treat a sick child." Pediatrics and geriatrics can both, of course, be learned by trial and error, but we attempt to limit this process by prior instruction.

Neglect of Geriatrics

Much of the neglect of geriatrics arises from unspoken "agism"—the old are naturally infirm, their infirmity is biologically ordained, their intellect shares in the decline, they are medically uninteresting to active practitioners, and—until Medicare—they were financially unprofitable. Students who formerly required attitudinal treatment against racism now require it against this culture-based folklore. Alter the attitude that sickness and confusion are idiopathic consequences of the passage of time, and expose a student to an experience of the highly dramatic effects of proper diagnosis and treatment, or the simple withdrawal of ill-judged medication, on the clinical features of old age, and both his professional mettle and his human concern will respond if they exist. Geriatricians are in fact more accustomed to dramatic symptomatic cure than pediatricians.

Most of us now in practice realize that age-dependent problems make up much of our office load, and that their preponderance will grow as the proportion of patients over 65 rises to around 17 percent of the population by the year 2000. Courses in geriatric medicine and geriatric psychiatry, when they are held, attract large numbers of experienced physicians who reckon they can use any help they can get. Once the attitudinal change has been made and ill health in old age

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is seen to require diagnostic explanation, there is no mystique about geriatrics, though for reading it is necessary to turn to standard European works such as those of Brocklehurst[3] or Hodkinson.[2] Neither the standard textbooks of medicine, nor, incidentally, the information sheets issued by drug manufacturers, recognize the last third of the human life cycle.

Principles of Geriatric Medicine

The principles involved in conversion from adult to geriatric medicine are simple. We teach them to students as Hippocratic aphorisms. Basically they can be stated as follows: No symptomatology is due to the passage of time alone. But the presentation of major disorders with age becomes increasingly nonspecific, so that the alerting clinical features that we have learned to recognize are absent—coronary heart disease, pneumonia, thyrotoxicosis, myxedema, osteomalacia, electrolyte imbalance and many other treatable conditions may present with no symptoms except mental blunting, loss of activity, and feebleness. Most old people are "well" despite minor continuing pathologic conditions, but in the minority—the evidently unwell—diseases are almost always multiple and the search for unitary causation is misplaced. The old do not normally "decline" in intelligence or mental capacity (only in speed of performance), and although chronic brain syndrome may occur, either through multiple infarcts or through the group of diseases which cause cerebral atrophy, most "dementia," especially when its onset is relatively rapid, is symptomatic. The syndrome of senility, composed of feebleness, mental deterioration, loss of mobility and interest, and eventual death, is not a diagnosis, but the equivalent in geriatric medicine of "failure to thrive" in pediatrics.[2] It calls for energetic investigation, with special attention to the medications the patient is receiving, because about a third of such presentations are wholly or largely iatrogenic and induced by doses (for example, sedatives or antihypertensives) that in adult practice would be trifling. Because of this high susceptibility to drugs and the lowering of the therapeutic index, where multiple pathologies exist not all of them can or should be treated. Management accordingly poses an extremely challenging test of clinical judgment; diuretics, sedatives of all kinds (often ordered to suppress the confusion resulting from undiagnosed endocrine or cardiac disease, or infection, or to "treat" the normal pattern of light sleep in older people) and antihypertensives are the drugs most often overused. Any medication that induces microsomal enzymes can also induce "senile rickets" with its attendant weakness. Watch must also be kept for long-term, unreviewed medication and the borrowing of drugs from neighbors, as well as use of over-the-counter remedies of many kinds, and alcohol. In every case presenting as senility the review and usually the suspension of medication is an initial diagnostic, and not infrequently a curative, step.

Old people do not become crazy because they are old. They have the psychiatric disorders common to humans, plus two problems peculiar to age: the ease with which mentation is disturbed by pathology or medication, and the negative inputs from society. The commonest "senile" psychiatric disorder is not dementia but unrecognized depression, which can simulate it. Every case of psychiatric disorder in age requires first to be assessed as a medical problem, and every medical case requires some supportive psychotherapy—be it only contact with a doctor who does not inwardly fear and despise the old—to restore self-respect and neutralize the culturally prevalent custom of premature social burial.

Scenario for Geriatrics in America

Old people now are better informed, better educated, and higher in expectation—social, political, sexual, financial and medical—than were their predecessors. Their demands for access to modern geriatrics will have to be reckoned with. To a European, the outlook for geriatric medicine in America is alarming, however, out of self-interest. There is a risk that when political pressure generates the first vestiges of a proper health service, no matter how it is fiscally arranged, the demand for "geriatricians" will suddenly be made actual. Since there will be no trained staff to fill it, it will be met by improvisation, and when the results of this are seen, public pressure will lead to the wholesale "headhunting" of Europe, with serious damage to the geriatric services that have trained personnel for home use.

The solution is to train American geriatricians now, and the initial step is the creation first of a cadre that can teach and then of centers of excellence. The numbers required are small, but they need to be sufficient to establish a full experience of geriatrics as part of the intern curriculum, as is now being done, for example, at the

Long Island Jewish Hospital or the University of North Dakota. In the initial stages exchange fellowships could play a major part, with benefit both to Europe and to America.

Most American physicians are not consciously anti-old, any more than many old-time liberals were consciously anti-black. To get geriatrics off the ground we have to attack the cultural assumptions of humane and professional people; this can be done by instruction, but it is far more cogently done by demonstration. The return to vigor of a few "senile" patients under proper management is a spectacle that the average physician, if he has never seen it, will find profoundly consciousness-raising at a professional level. Geriatrics in Europe has thrived in part because students, knowing that they will not need to waste time functioning as entrepreneurs and tradesmen, can devote their energy to functioning as physicians, and it is to physicians and their self-esteem and expertise that geriatrics presents such a rewarding challenge. It is one that should be in line with the change in the social estimate of medicine and the spirit of self-questioning that I meet among young Americans now in medical school.

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Growth of the Eye

THE GLOBE of the eye is approximately fully grown at age three. The eye grows from 16 mm to approximately 23 mm during the first three years. It grows a tenth of 1 percent for the next ten years, so a 3-year-old child has approximately a fully mature eye.

—DAVID HILES, MD, *Pittsburgh*

Extracted from *Audio-Digest Ophthalmology*, Vol. 15, No. 14, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, Ca 91206.

Refer to: Manning PR: Continuing medical education in midpassage (Medical Education). West J Med 128:260-265, Mar 1978

Continuing Medical Education in Midpassage

PHIL R. MANNING, MD, *Los Angeles*

Mandatory continuing education for physicians and other health professionals raises numerous problems. Issues that were considered academic when continuing education was voluntary now take on major practical and political significance. There is the risk that future legislation will mandate activities and methodologies which have not been proven. Research and development in continuing education must be accelerated so that decisions can be based on proper data. Centers of research and development should be established to encourage research and provide a sound foundation for the future of continuing education.

For good or ill, formal continuing education is now a fact of medical life, required by the legislatures of an increasing number of states, including California. Because it is mandatory, a number of issues have now become pressing that were formerly of academic interest alone. These issues will have a significant impact on all practitioners.

Until quite recently the degree of participation in continuing education was decided by the individual physician and, to some extent, by his professional society. As recently as 1955 Vollan stated, in an assessment of continuing medical education: "Since the public has seen fit to allow the profession to control its own affairs, it is the responsibility of organized medicine to insure the constant continuing education of its members." Dr. Vollan went on to say: "In the last analysis, however, it is the individual physician's responsibility to society to insure his own constant fitness to practice medicine at the highest possible level, which requires that he continue his education regularly throughout his career."[1] Now, two decades later, society is beginning to require proof that this responsibility has been met .

Shifting Responsibility for Continuing Education

Thirty years ago the American Academy of General Practice became the first medical organization in this country to require participation in continuing education as a condition of membership. The Voluntary Physician Recognition Award by the American Medical Association was implemented in 1969. The same year, the California Medical Association initiated a voluntary pro-

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gram granting certification for approved continuing education. Mandatory continuing education for membership in state medical societies began in the State of Oregon in December 1970. At present medical societies in 15 states and the District of Columbia require continuing medical education as a condition of membership (Alabama, Arizona, District of Columbia, Florida, Kansas, Maine, Massachusetts, Minnesota, Montana, New Jersey, New York, North Carolina, Oregon, Pennsylvania, South Dakota and Vermont).[2] Medical practice acts in 17 states give their respective state boards of medical examiners authority to require evidence of continuing medical education as a condition for reregistration of the license to practice medicine (Alaska, Arizona, California, Colorado, Illinois, Kansas, Kentucky, Maryland, Michigan, Minnesota, Nebraska, New Mexico, Ohio, Rhode Island, Utah, Washington and Wisconsin).[2]

The mandate for formal continuing medical education is based on the presumption that some physicians, at least, have not continued their education and that continuing education will improve health care.

Relationship of Continuing Medical Education and Patient Care

Health care is a very complex endeavor. Besides the appropriate application of skills and knowledge, components of patient care include accessibility, availability, acceptability, affordability, continuity, prevention and comprehensiveness.[3] Quality of patient care is contributed to by many professionals, administrators and workers in addition to physicians, nurses and pharmacists. The totality of care is greater and more complex than most of us realize. It is a team effort. It is profoundly difficult to evaluate. Continuing education for physicians cannot by itself be expected to alter dramatically all the multiple problems of patient care.

For many years, patient care was believed to be governed almost entirely by physicians' competence in diagnosis and therapy. Recently, it has been realized that a physician's diagnostic and therapeutic skills are major but not exclusive ingredients of excellent patient care. With this realization, some writers have overreacted, tending to downgrade the importance of the competence of a physician in diagnosis and therapy. It is essential to continue to stress physician competence and skill, if patient care is to continue to improve.

From the standpoint of physicians, we can look at the problem in still another dimension. We can compare a physician's competence (that is, what he is able to do) with his performance (that is, what he actually does in a particular situation). Drs. Clement Brown and John Williamson are major pioneers who have found that many, if not most, patient care problems they have encountered in their extensive work in community hospitals are related to administrative and organizational problems rather than to lack of knowledge.[4,5]

It is therefore necessary to keep in mind that there are some unrealistic expectations about what continuing education can achieve, but this should not obscure the fact that some expectations relating to the competence of physicians in diagnosis and therapy are realistic and that continuing education can play an important role in this area. Properly conducted continuing education can alert a physician to significant new advances in medicine and help him to review important fundamental concepts. The physician can share and gain from the experience of experts. He can ask questions about specific patients under his care. He can gain direction for self study. He can renew the academic spirit and approach his practice with increased enthusiasm. As Professor Cyril Houle has said, "While continuing education will not cure all the problems of the profession, without it no cure is possible."[6]

Issues in Continuing Education

There are several issues to consider in mandatory continuing education for physicians:

- What types of education experiences are and should be acceptable to meet requirements?
- Who should be the purveyors or providers of continuing education?
- What should be taught and learned?
- What are the costs of continuing medical education?

What Types of Education Should Be Acceptable?

There is a persistent idea that continuing education must be defined as a classroom activity. The Physician's Recognition Award (PRA) of the American Medical Association (AMA) requires a total of 150 credit hours over three years with a minimum of 60 credit hours in Category 1 (See Table 1).[7] The regulations appear to foster various types of educational activities; however, those

TABLE 1.—*Summary of Criteria for the American Medical Association's Physician's Recognition Award*

Category		
1	CME activities with accredited sponsorship	No limit
2	CME activities with non-accredited sponsorship	45 hours
3	Medical teaching	45 hours
4	Papers, publications, books and exhibits	40 hours
5	Non-supervised individual CME activities	45 hours
5a	Self-instruction	(22 credit hours)
5b	Consultation	(22 credit hours)
5c	Patient care review	(22 credit hours)
5d	Self-assessment	(22 credit hours)
6	Other meritorious learning experiences	45 hours

CME = continuing medical education

which must be validated are considered Category 1. These are formal and didactic, and usually classroom approaches.

Legislators have had practical difficulties in determining which components of continuing education to make mandatory. It is very difficult to validate that a physician has read a particular journal or that he has listened to a particular tape or, most important, that he has studied about specific problems of his own patients. If he is a captive student in a classroom one can at least verify his attendance.

The need for verification is, of course, based on the presumption that the professional will not be accurate in reporting his activities and will not be aggressive in studying individual problems that occur in his own practice. Many within the profession feel that the whole hierarchy of categories imposes bureaucratic requirements which are not in keeping with the ethics of a scholarly profession.

In fact, many feel that the requirement to attend formal programs may stifle interest in self-education—that a physician may feel, "I have done my hours for the year and therefore have no further educational requirements." The requirements for study should relate to the need for study as directed by actual problems in the physician's practice. This most important aspect of continuing education is difficult, if not impossible, to verify, let alone mandate.

Who Should Provide Continuing Education?

Since 1967 the Council on Medical Education of the American Medical Association has accredited providers or purveyors of continuing medical education. The standards developed have been used by state medical associations so that they in turn can carry out surveys and accredit activities locally, with ultimate action and decision by the Council on Medical Education. This has led to the beginning of a national standard of accreditation for purveyors of continuing medical education.

TABLE 2.—*Composition of Liaison Committee on Continuing Medical Education*

American Board of Medical Specialties	3 members
American Medical Association	4 members
American Hospital Association	3 members
Association for Hospital Medical Education	1 member
Association of American Medical Colleges	3 members
Council of Medical Specialty Societies	3 members
Federation of State Medical Boards	1 member
Federal representative	1 member
Public representative	1 member

The Liaison Committee on Continuing Medical Education (LCCME), formed in 1975 and working through the Coordinating Council on Medical Education (CCME), is a national organization which in July 1977 replaced the AMA in accrediting providers of continuing education.[7] The LCCME has representatives of its eight parent organizations and of the public at large (See Table 2).

Presumably, this organization will be the major accrediting agent of all purveyors. In the early stages, criteria for accreditation should be similar to the AMA criteria. However, the LCCME has no authority over state legislatures who may wish to preserve the right of accrediting purveyors for themselves via boards of quality assurance. Consequently, difficulties may arise in the future in identifying valid purveyors.

Purveyors of continuing education include medical schools, medical societies, community hospitals and organizations such as pharmaceutical companies. Medical schools, which many feel should be the hub of continuing education as they are in undergraduate education, are not formally dominant in continuing education. Specialty societies can maintain a more dominant posture, as they deal with a membership which is relatively small and eager. Their advertising costs are lower than a medical school's and they have the great advantage of not having to pay faculty salaries. Instead, for a nominal honorarium they can obtain the services of a faculty member for a few hours, whose yearly salary is paid by the medical schools. In addition, courses offered

TABLE 3.—*Approved Category 1 Hours Reported by Physicians to the Certification Program of the California Medical Association*

	1969	*1975*	*1976*
Hospital	13,000	1,827,377	2,038,929
Specialty societies	67,000	334,793	479,205
Medical schools	64,000	240,791	302,595

by specialty societies often are looked upon as more prestigious that those offered by medical schools.

Community hospitals are in a strong position to organize continuing education for their staffs. Physicians congregate there each day; they have record systems and personnel who can assess records to determine educational and administrative needs. Table 3 shows the tremendous growth of community hospitals as locations for approved continuing education in California.[8] Unfortunately, hospitals usually do not have a formal faculty and must depend on the abilities of local practitioners, often supplemented piecemeal by faculty members from nearby medical schools.

These provider groups are, however, interdependent. A major contribution to continuing education may come through coordinating the activities of medical schools, medical societies, community hospitals and pharmaceutical companies. The ideal relationship has yet to be conceived, let alone implemented, but a rich opportunity exists for developing a cooperative organizational structure for the common good.

What Should Be Taught and Learned?

Several simple approaches help to determine the most significant issue: what to teach and learn. Many organizations use questionnaires to ask persons who attend formal courses what subjects they would like to hear discussed, and often they ask faculty members what practicing physicians should be taught. There are limitations to these methods: a physician may ask for subjects he likes but may not need and a faculty member may wish to display products of his research, which have little application to practicing physicians.

There are more precise ways to determine educational needs. For example, the specialty boards and the National Board of Medical Examiners can provide information on how physicians are scoring on various test items, so areas of weakness can be emphasized. Health statistics, both regional and national, can be used to better advantage. Leading physicians who act as major consultants in their community can be interviewed systematically to determine problems referred by physicians. All of these methods can be useful and all are underutilized.

A still better approach to an individual physician's needs is accurate determination of his performance. Audit procedures as they are being carried out may be valuable to determine administrative, organizational problems and problems of documentation, but are often not adequate as a basis for education. More research is needed to better identify educational needs and to satisfy these identified needs.

What Are the Costs of Continuing Medical Education?

The costs of providing continuing medical education have risen in recent years due to inflation, particularly in mail advertising and administration; payment to faculty has not been inflated to the same extent. These costs are reflected in tuition charges. However, the main cost to the practitioner is not tuition itself, but the expense of an office which must be maintained whether the physician is working or not. Time away from practice is clearly a major expense item. Miller estimates that the cost of physician time in continuing education is about $1.4 billion dollars annually in the United States. Even though this estimate includes time that would not be spent in seeing patients, the figure dramatizes the potential cost of physician time in continuing medical education.[9]

Those interested in continuing education must realize that a physician who comes to a postgraduate program is paying a very significant price, not only in tuition, but by losing income while his office expense continues. Most physicians and the public feel that it is proper for physicians to shoulder the cost of continuing education.

What Are the Frontiers for Development?

In the course of designing and implementing concepts of continuing medical education, several additional major issues or frontiers need to be studied carefully:

- Improvement of existing educational activities.
- Educational television satellite.

- Identification of educational needs and provision of feedback.
- Use of computer technology.

Improvement of Existing Educational Activities

Since continuing education activities are no longer voluntary but are mandatory, there is an obligation on providers of physician education. There is also a burden of obligation on those who have passed laws. The physician must participate in formal education. It is no longer his choice. We, therefore, have no choice but to do things better than we have ever done them before.

The move toward better formal continuing education has started. In standard classroom programs there has been a trend to improve technical aspects of instruction, to organize programs by behavioral objectives, to emphasize better audiovisual content, to improve material to be handed out, to select faculty who are good speakers and to involve physicians in active learning such as problem solving activities.

Educational Television Satellite

As the new educational television satellite program being coordinated by the Lister Health Center becomes available, many of the things we traditionally have done in the classroom can be done equally well via a medical television network.[10] This could cause a major change in traditional classroom programs throughout the country. The impact might be as significant as the effect of sound motion pictures on vaudeville and could result in a complete restructuring of the classroom experience.

Identification of Educational Needs and Provision of Feedback

Despite the attraction of satellites and the challenge of devising new ways to package classroom education, more important and fundamental issues await consideration. How can we perfect a system to identify needs and develop a nonpunitive feedback mechanism, which will help a physician profit from his own experience while learning about his practice?

The difficulty with developing a feedback mechanism in medicine is that society is perceived to be, and often is, critical and harsh when it comes upon an error by a professional, either in judgment or in fact. This is a major limiting factor in developing a proper feedback mechanism. In its desire to see things go perfectly, society will undoubtedly overreact to shortcoming, punish the physician who made the error and make it altogether inadvisable for him to expose himself. I am not concerned solely about the welfare of a physician in a punitive situation, although he has a difficult job and needs support. I am concerned that medical care will suffer. When a person is defensive and guarded, real issues are obscured and therefore it is impossible to solve real problems.

A nonpunitive feedback mechanism has a much greater prospect for long-term success because a physician need not be defensive. He is able to find out his problems and react to them without undue criticism or punishment. Therefore, it is imperative to develop a feedback mechanism responding to identified needs. This mechanism must be nonpunitive, not just for the good of the physician but for the good of health care. A physician must look openly at things he does with the motive to improve his competence and performance in dealing with patient problems. His attention should not be diverted by threatening, criticizing, punishing regulations or mounds of irrelevant paper work. This is a crucial issue which must be faced at every step of medical education.

Using Computer Technology

At present, formal continuing education for the physician is being pursued from two fundamentally different approaches. We teach a physician facts in traditional postgraduate courses so that at the proper time, perhaps weeks or months later, he may recall them and carry out an activity in response. We may notify him retroactively of problems that are derived from audit. This latter procedure usually applies to groups of physicians.

An advance in continuing education is now possible through the technology of computers, which will make available information to help solve a problem of diagnosis or management at the time a physician identifies the problem. In other words, it is now possible to weave continuing education into office practice or hospital practice by having a computer terminal as part of the practice environment. Dr. Lawrence Weed has developed a computer program and system now being tested on the medical floors at the University of Vermont. This system, among other things, allows a physician to review displays that help him form treatment plans at the time he is solving his diagnostic and therapeutic problems. Many other partial systems are being developed that utilize

computers. Immediate continuing education based on real problems at the time that diagnostic and therapeutic plans are formulated should become a reality. Old habits are hard to change and the use of computers will, of course, be resisted by some. Some legal and social problems, such as patient record confidentiality and central control of patient care, will need to be solved. Still, the computer as a tool can make possible immediate continuing education on real issues. This is an objective worth striving for.

The Need for Centers of Research and Development

No issue in education is more important than continuing education in the professions. All the professions need better methods of continuing education. As for medical continuing education, efforts should be made to develop several research and development centers around the country to develop and test ideas and approaches in continuing education for health professionals.

Since strong and well-motivated desires to see things get better and get better quickly may pressure state legislators to mandate educational activities that are ahead of the state of the art, it is essential to test methodologies and approaches before legislation goes further. Research and development in this field can give us data on which to base such legislation. For the present, we should be content to improve our methods to comply with current requirements to the best of our abilities. But we must press for accelerated research and development before further laws and regulations mandate methods whose validity needs to be substantiated. Those who pass laws mandating educational activities and those in medical education have a profound responsibility to foster further research to define and develop educational principles and methods that will aid the physician and other health professionals to offer ever-improving health care.

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Special Article

Refer to: Felton JS: Legal implications of physical examinations. West J Med 128:266-273, Mar 1978

Legal Implications of Physical Examinations

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With the new national emphasis on the prevention of occupationally incurred disease, legislative constraints have been placed in connection with the medical examination of employed persons at health risk. Concurrently, there is mandated a system of communication to the worker of the significant clinical findings encountered on his physical and laboratory inventories.

> *. . . laws have been passed in well-ordered cities to secure good conditions for the workers; so it is only right that the art of medicine should contribute its portion for the benefit and relief of those for whom the law has shown such foresight . . . .*
>
> BERNADINO RAMAZZINI, 1713[1]

EXAMINATIONS OF EMPLOYEES have been characteristic components of programs in occupational medicine since industry was first made apprehensive by the passage of workers' compensation laws. Performed initially as a screening device to guarantee a disease-free and injury-free work force with the hope of lightening the burden of liability, the review of applicants for work became a part of the selective placement process generated during World War II. With current legislation demanding greater utilization of the physically and emotionally limited job candidate, the examination has become a mechanism for establishing a health baseline on entry into the work scene rather than a method of excluding marginal persons. In addition to the use of the examination at time of hire, industry has been accustomed to the periodic reevaluation of the incumbent employee to assure itself that the work in no way has proved detrimental to his health.

This clinical function has not been solely the task of physicians who work fulltime with a work force. Innumerable practitioners who provide primary care are asked by industrial and business firms to examine new or present employees, either on part-time at the worksite or in their offices under a retainer or a fee-for-service agreement. That there are now new legal implications in this professional undertaking must be understood by all physicians who are involved.

The early concepts of periodic health appraisal, like the legal demands to emerge later, were not generated from within the medical profession, but found their inception and first practical application as part of the business and welfare activities of life insurance underwriters. Policy holders of the Provident Savings Life Assurance Society were

Presented at the 106th Annual Session of the California Medical Association, March 5, 1977, Anaheim.

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The opinions and assertions contained in this report are the private ones of the writer and are not to be construed as official or as reflecting the views of the Navy Department or the Naval service as a whole.

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offered examinations in 1911, and in 1914 the Life Extension Institute was created.[2] The American Medical Association did not join the so-termed movement until 1922, when a committee was created by resolution to study the issue.[2]

Background

Certain types of examinations have been mandated for decades so that the health of the public can be maintained. In California, as in other states, specific statutes have granted health officers the power of examination of persons with infectious tuberculosis[3(§3285)] and venereal disease.[3(§3191)] Reports of the examination of persons with convulsive disorders have been required,[3(§410)] and the examination of food handlers may be requested.[3(§28688),4(§10734)] Certification of the physical condition of boxers and wrestlers just before a bout is demanded by California state code,[5] and minors seeking work permits must be examined.[6]

All hospital employees having contact with patients or with materials used by patients must have preplacement and periodic health evaluations including skin tests,[4(§53,273,70723)] and teachers at the elementary, secondary and community college levels are required to have an x-ray study of the chest or skin test before employment, and quadrennially thereafter.[6(§11708)]

Medical examination is needed by adoptive parents in California.[4(§30673)] Those employees exposed to ionizing radiation and who wear film badges must undergo bioassay procedures and medical review if overexposure (ten times permitted level) occurs.[7] In certain questionable situations in restaurant operation, medical evaluation of the food handlers may be sought.[3(§28688)] In some jurisdictions, food handlers, milk handlers, teachers, child care workers and those persons treating, caring or cooking for others are subsumed under the designation "sensitive occupations," and may be subject to removal from work —examination being implicit before such action— when they manifest communicable disease or are in contact with such disease.[8] In well over 20 states, physicians examine inebriates under a form of the Uniform Alcoholism and Intoxication Treatment Act.[9]

Applicants for certain forms of public assistance, particularly persons who are alleging disability, must be reviewed, by law. Drivers of motor vehicles in California wishing class 1 or 2 drivers' licenses must meet the medical requirements of state statutes and those standards delineated by the Federal Highway Administration of the Department of Transportation.[4(§100.10,100.11),10]

In the public sector, at the federal level, in the Department of the Navy, for example, operators of vehicles transporting explosives or hazardous material must be examined,[11] as well as those persons assigned to duties involving the operation of construction and weight-handling equipment.[12] Federal law governs the examination of flight personnel who seek airman certificates[13] and, of course, draftees and career military personnel brought into the armed services have traditionally undergone rigorous medical examinations.

The regulations supporting these medical evaluations, as indicated, have been codified for decades, and present little that is new. Society, however, has promulgated protective legislation so that more detailed examinations are mandatory in numerous work situations.

Variety of Examinations

Occupational physicians or physicians who carry out examinations for industry may do many different types of examinations, as dictated by company policy, type of industry, spectrum of jobs, needs of benefits plans, use of motorized equipment, kinds of health-hazardous exposures present, capability of the in-plant medical service, and loci of operations (local, national, multinational). The examinations conducted will relate to persons undergoing employment, promotion, retirement, termination, transfer, return-to-work or retention of employment; to persons in potentially stressful or health-threatening occupations; to persons in positions of public responsibility involving watercraft, or motor vehicle operation, commercial or industrial air transport, or the operation of fixed or mobile powered equipment; to persons undergoing official travel or change of station, particularly to locations abroad; or to persons undertaking work involving considerable financial investment (leaders in the entertainment industry or corporate business). Not every examiner will complete all of the broad selection of health reviews, but depending upon the industrial affiliation, most will see certain employees in one or more of these categories.

In many situations, the reports of findings will remain with the examiner. If the appraisal is done by a specialty consultant or a physician extramural to the company, a report will be forwarded to the medical director of the requesting organiza-

tion. In every instance, diagnostic information will remain privileged, and only a communication interpretive of the conclusions and helpful to the formulation of an administrative decision will be relayed to the requesting unit.

Not all of these evaluations are required by law, but many have been specified by legislative action or implementing directives.

Examinations for Employment

The purposes of such examinations, as noted previously, have changed over the years from their serving as organizational protective devices, to instruments for good manpower utilization, to statements of health status for use in future comparisons. While there has always been wide variance in both the scope and quality of such examinations, and while the application of the conclusions has made or nipped many useful careers, it is only in the past few years that employers have been directed to conduct such examinations on entry of candidates into work situations.

The earlier of the modern pieces of federal legislation that address the issue of medical examinations is the Federal Coal Mine Health and Safety Act of 1969,[14] as amended by the Black Lung Benefits Act of 1972.[15] Under these laws, any person beginning work in a coal mine for the first time, as soon as possible after commencing employment shall have an x-ray study of the chest. These roentgenograms will be taken in accordance with specifications prescribed by the Secretary of Health, Education, and Welfare (HEW), and will be supplemented by such other tests as deemed necessary by him. Further, the films will be read and classified in the manner prescribed by the Secretary of HEW, and the results of each interpretation will be submitted to the Secretary of Labor, the Secretary of HEW and, at the miner's request, to his personal physician. In the Amendments to the Act, additional relevant evidence such as blood gas studies, electrocardiograms, pulmonary function studies, physical performance tests and medical history data will be used in adjudication of a claim.

To assure expertise in the review of the chest radiographs, examinations have been held for the establishment of radiological proficiency in interpretation. During the first round of medical examinations conducted under the Act (August 1970 through December 1971), two physicians interpreted the roentgenograms, using the UICC/Cincinnati system for the classification of pneumoconiosis.[16] They were considered qualified by virtue of professional emphasis or special training. Between the first and second rounds of examination (the second beginning in July 1973 and ending in March 1975), the ILO-U/C system[17] became available, applicable to all types of pneumoconiosis, not only coalworkers' pneumoconiosis. Reporting was accelerated and epidemiologic studies were broadened.

Subsequently, it was decided to clarify uncertainties in the diagnosis of complicated pneumoconiosis and other large opacities; the first testing procedure was limited to simple pneumoconiosis. Based on the experience gathered from the first two rounds of examinations, a revised proficiency examination has been designed to evaluate the prospective interpreter's skill in classifying all large opacities and the other possibly significant findings applicable to the interpretations of all respiratory diseases, according to a letter from P. Popovich, in February 1977. A second interpreter examination is about to be held "to test the proficiency of physicians to interpret chest roentgenograms for interstitial disease and particularly to classify the profusion characteristics of roentgenograms of the chest for the pneumoconioses." It is anticipated that there may be nearly 50 physicians qualifying, who in a fourth of their time could carry out 2,000 readings each a year. The present case load is 100,000 cases per year, but could double in the future, as estimated by R. Morgan in a written communication, February 1977.

The reason some clarification has been given here regarding the method of physician selection and the use of classifications schemes is that the procedures illustrate the extension of federally mandated examinations to the responsibility of, and the performance of, those practitioners carrying out the examinations. In fact, in the federal standard for coke oven emissions—the standards are to be discussed shortly—it is stated that the examinations will include a 14 by 17-inch posterior-anterior chest x-ray film *and* the ILO-U/C rating.[18] This area of medical enterprise may be predictive of other efforts to improve professional reliability.

The more recent mandate passed by the Congress was, of course, the Occupational Safety and Health Act of 1970,[19] in which the Secretary of Labor was authorized to promulgate occupational safety and health standards. The standards are

based on criteria data furnished by the Secretary of HEW, and as developed by the National Institute of Occupational Safety and Health (NIOSH). To date, certain standards have been produced, primarily for asbestos, vinyl chloride, 13 carcinogens, and coke oven emissions.[18] A 14th standard, MOCA or 4,4′-Methylene bis (2-chloroaniline) has been dropped from the federal listing, but has been retained in California. On passage of a federal standard, a state, via its own plan, has six months in which to promulgate a standard. Currently, plans are operative in 23 states and the Virgin Islands, the federal government having jurisdiction in the 27 other states and Puerto Rico. In the West, only Idaho and Montana are under federal regulations.

The standards relate closely to preemployment physical examinations, for such evaluations are obligatory under the Law. For example, in the standard for asbestos (§1910.1001) under *Medical Examinations,* it is stated:

(1) *General.* The employer shall provide or make available at his cost, medical examinations relative to exposure to asbestos . . .

(2) *Preplacement.* The employer shall provide or make available to each of his employees, within 30 calendar days following his first employment in an occupation exposed to airborne concentrations of asbestos fibers, a comprehensive medical examination, which shall include, as a minimum, a chest roentgenogram (posterior-anterior 14x17 inches), a history to elicit symptomatology of respiratory disease, and pulmonary function tests to include forced vital capacity (FVC) and forced volume at one second (FEV_1).

The comparable wording for most of the carcinogens covered by the standards reads as follows:

Medical Surveillance. At no cost to the employee, a program of medical surveillance shall be established and implemented for employees considered for assignment to enter regulated areas, and for authorized employees. (1) Examinations. (i) Before an employee is assigned to enter a regulated area, a preassignment physical examination by a physician shall be provided. The examination shall include the personal history of the employee, family and occupational background, including genetic and environmental factors. . . . (iii) In all physical examinations the examining physician shall consider whether there exist conditions of increased risk, including reduced immunological competence, those undergoing treatment with steroids or cytotoxic agents, pregnancy and cigarette smoking.[18]

There are further requirements attendant upon the examinations. Referring to the standard for asbestos, once again, it is stated that medical records shall be retained by the employers for at least 20 years; in chromium exposure, the recommended required period is 30 years. Further, the contents of the examination records shall be made available for inspection and copying to the Assistant Secretary of Labor for Occupational Safety and Health, the Director of NIOSH, or their authorized physicians and medical consultants, and on request of a current or former employee, to his physician. The examiner shall provide the employer with a statement of the employee's suitability for employment in the specific exposure.

Records in connection with the examination of those exposed to carcinogens shall be maintained for the duration of the worker's employment, and upon termination, including retirement or death, the records shall be forwarded to the Director of NIOSH.

The standard for vinyl chloride is considerably more specific calling for a history covering alcohol intake; a past history of hepatitis; a work history and past exposure to potential hepatotoxic agents, including drugs and chemicals; a past history of blood transfusions, and a past history of admissions to hospital. Utilizing serum specimens, determinations shall be made of total bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and gamma glustamyl transpeptidase. The examiner will devote specific attention to detecting hepatomegaly, splenomegaly or nephromegaly; to dysfunction of those organs and to abnormalities of the skin, the connective tissues and the pulmonary system.

When these procedures show abnormal findings, they should be repeated within three to four weeks, if not sooner. If the abnormalities remain, the employee should be withdrawn from contact with vinyl chloride, while a more comprehensive evaluation is conducted. Suggested are urinary sediment studies, pulmonary function measurements, x-ray studies of the chest, additional enzyme determinations, protein electrophoresis, liver scanning and hepatitis B antigen testing.

The above desiderata are those items provided in an enforceable code. Comparable requirements are given in approximately 44 criteria documents* prepared by the Director of NIOSH; these documents may be used in court solely in the form of supporting evidence in contested cases. The criteria documents provide for similar examinations, with the specifics varied in accordance with potential physiologic or anatomic alterations. While the earlier documents were more generic

*The criteria documents are titled, for example, *NIOSH Criteria for a Recommended Standard . . . Occupational Exposure to Chromium (VI).* Several more are expected shortly as finished publications.

in their medical surveillance requirements, the more recent criteria call for the completion of certain pertinent diagnostic or laboratory procedures. Additional criteria documents appear regularly, but their conversion to standards has been slow.

A case appeared in which an Occupational Safety and Health Administration compliance officer cited a company for six violations, two being contested by the company. At a hearing, OSHA testified that examinations had not been provided for employees exposed to airborne concentrations of asbestos fibers. The company argued that the levels were so low that medical examinations were not necessary. The Review Commission upheld the judge's decision that the presence of *any* concentration of fibers required the conducting of medical evaluations. Although the citation was affirmed, no penalty had been proposed.[20]

No case has been encountered wherein an employee had refused the examination. The employer is only mandated to offer the evaluation. The employee may, however, decline on religious grounds, except where examinations are necessary for the protection, health or safety of others.[19] In the absence of an examination, should the employee be permitted to continue working? There has been no satisfactory answer to this question, as yet.

In jurisdictions where law enforcement or fire suppression personnel are employed, the issue of mandatory annual physical examinations has been questioned. By precedential law, it has been determined that employees whose duties include arduous physical tasks could be required to undergo annual medical examinations, as reported in a 1973 communication from L.A. Curtis to R. Houts.

Examinations During Employment

In the periodic examinations called for by the standards the interval between appraisals is spelled out. Asbestos workers, for example, must be examined annually, as are employees in contact with agents suspected of being carcinogenic. The same interval holds for vinyl chloride workers, but persons engaged in such work ten years or longer will be examined every six months.

As stated, the criteria documents offer recommendations. The conversion of recommendations to mandated examinations is anticipated by such wording as "Initial annual examinations for presently employed workers shall be offered within six months of the promulgation of a standard incorporating these recommendations."

In the event, of course, of an emergency—unanticipated or untoward worker-substance contact—the worker shall be afforded appropriate medical surveillance.

To assure oneself that the examinations conducted and the periodicity followed are in compliance with either the standards or the criteria documents, the mandates or recommendations must be consulted directly. The standards are available from the local OSHA Office (Department of Labor), and the criteria documents, published by NIOSH may be obtained from the Superintendent of Documents, United States Government Printing Office, Washington, DC, or local sales offices.

It is customary in nearly every civil service jurisdiction for a supervisor, because of an employee's impaired job performance, to request a fitness-for-duty examination or a medical reevaluation of that worker. The physician is asked, in light of the physical and environmental demands of the job, to determine if the person is able to carry out the duties called for in his job description. In the federal jurisdiction, the employee may have the evaluation conducted by his private physician. In most instances, the resultant opinions rendered are statements strictly in keeping with the patient's wishes and do not reflect either an objective review or a sound judgmental conclusion.

These procedures are mentioned because the implementing regulations are quasi-legal, and the conclusions may determine a worker's continuation at work, his reassignment or his retirement. Many private firms follow the same practice, but require the evaluations to be completed by the company's own medical personnel.

Examinations on Termination of Employment

In nearly all instances, repeat examinations comparable to those on entry are called for on separation from employment, with the records to be retained for a specified length of time.

Communication of Information

The days of keeping employees uninformed insofar as medical information is concerned have long disappeared with today's legislation. While OSHA 1970 does not speak directly to the point

of informing an employee of the results of his examination, such transfer of information is implicit in the authorized forwarding of examination findings to personal physicians. The concept is given additional substance by the Act which calls for "the education and training of employers and employees in the recognition, avoidance, and prevention of unsafe or unhealthful working conditions," and consultation with and advice to "employers and employees, organizations representing employers and employees as to effective means of preventing occupational injuries and illnesses."[19] The asbestos standard also provides that an employee be notified within five days and in writing of any exposure to airborne concentrations of asbestos fibers in excess of the prescribed limits, and of the corrective action being taken.

As employees are informed of the health hazards relating to a work material and the signs and symptoms of overexposure, it is normal for a worker to be concerned about his own examination results. He is entitled to a clear, understandable explanation of physical change, laboratory test values, functional performance levels and x-ray interpretations. This logical by-product of an examination may not be new to private patients; in many instances it has not been part of the follow-up of the examination given the prospective or incumbent employee. That this procedure is not permissive is given substance by the standard for coke oven emissions which requires a written opinion from the examining physician which shall include "A statement that the employee has been informed by the physician of the results of the medical examination and any medical conditions which require further explanation or treatment."[18] The American Medical Association has indicated that the first use of information derived from a physical examination should be in a discussion with the worker of his significant findings.[21]

The question of transmittal of information following examination has been tested in the courts. In cases which have been cited, a third party—employer or insurance underwriter—selects a physician to examine, for its benefit, job applicants or potential purchasers of insurance. Absent from these situations is a physician-patient relationship, wherein, expressed or implied, there is a contractual relationship, in which the physician will treat the patient with proper professional skill and the patient will pay for such treatment. There has been an increasing tendency, though, for the courts to hold in these situations that such a physician owes the applicant the duty of reasonable care, whether or not a physician-patient relationship exists. When the physician acts as a "company doctor," he need not disclose to the person examined his findings or the nature of the report ultimately to be made to the third party. If he chooses to discuss the findings, he must not mislead the applicant as to his actual condition.

If the report submitted is unfavorable, the physician's findings may be litigated. When diagnostic tests are ordered, the results should be reviewed carefully and a notation made as to whether such tests were discussed with the subject or the third party. The record should reflect also the reaction of the person on receiving the report as well as any follow-up action on the part of the physician to determine if his advice had been heeded. The applicant expects to be dealt with as if he were an actual patient.[22]

In a case in which a physician disclosed, without consent, medical information concerning his private patient to the patient's employer, it was ruled that the physician was liable for damages for breach of contract.[22] Disclosure presumably can be made only because of the supervening interests of society.[23] A governing factor is whether the physician undertakes to advise the person examined regarding his condition and misrepresents the subject's condition to him while concealing evidence that the person needs medical treatment. In these cases the physician has been found liable. As reported in a February 1977 communication from J. A. Gottlieb, a large award was made where the physician, employed by the plaintiff's employer, failed to advise the subject that he had asbestosis and should restrict his work activities. The question of liability in these instances does not seem to be settled.

Examinations Required by Employer-Union Contract

Management and labor reach agreement through the system of collective bargaining. Included in the contractual agreement are many provisions, some of which are designed to protect the health and safety of employees on the job. The Bureau of Labor Statistics, United States Department of Labor, studied nearly all agreements in the United States covering 1,000 workers or more, exclusive of those employees in railroads, airlines and government.[24] Of 1,724 pacts, 93 percent (representing 7,868,000 workers)

had some safety and health provisions. Clauses calling for company-paid medical examinations appeared in just under a third of the agreements examined. The terms of the provisions varied widely, speaking to examinations for job applicants, for all employees, or for specified groups of employees such as those workers exposed to hazardous work materials, or persons returning to work after illness or injury.

These data are cited because in an industrial setting, the language of the contract can supersede existing law toward greater stringency. For example, if under state law no examinations of framasite workers is required, but the bargaining union demands such reviews, the provision will be written into the contract, and such examinations will be provided.

Examination of Immigrants

A case in the author's experience deserves inclusion because of the legal implications. A professional engineer from a country in Southeast Asia sought admission to the United States, and in compliance with existing regulations[25] had obtained in his native city an exit physical examination, including an x-ray study of the chest. All findings were in order, presumably, and after a brief period in this country, he applied for a position. The prospective employer conducted a medical examination, and the chest radiograph disclosed active tuberculosis. When the films were compared with those he brought with him, it was readily seen that the "normal" films were not his, but had been purchased for the specific use of entry into the United States. Moral: Even though a candidate may be evidence-laden, important features of the preplacement examination should be repeated.

Ethics in the Examination Process

Plunkett[26] relates the story of an engineer applying for work who was given a preemployment medical history and a physical examination form, as well as a copy of the company's medical criteria, for transport to the physician of his choice for completion. The forms were returned to the Medical Director with the comment that, "Complete examination at this time is entirely within normal limits." The man was hired.

Late in the same year the engineer returned to his out-of-state surgeon for medical care. The following month, on inquiry, the medical department learned that the engineer had had a surgical operation for a neoplasm, and that the physician who certified the man's good health in the spring had carried out a surgical procedure six months before for an undifferentiated metastatic carcinoma. After five months of work, the employee died, the direct costs to the employer coming to $26,000. No peer review was obtainable of the perjuring practitioner.

Returning to another episode in the author's experience, the case is recalled of a young man who presented himself for employment, bringing with him a letter from a highly reputable local physician to the effect that the candidate was in peak health and could undertake any job which he would be offered. In the search for background medical information, a letter was seen, written by the same physician about the same person, addressed to the Selective Service System. In this communication, the man was depicted as having a broad variety of chronic and disabling conditions which, most certainly, rendered him unfit to serve in any military capacity. The letters were dated two weeks apart.

How does one retain confidence in any communication forwarded to the physician in industry from patently dishonest sources?

Workers' Compensation

As nearly every physician has treated injured workers, he or she knows that an examination, under the act germane to the jurisdiction, can be requested by the employer, the Administrative authority, or the patient. Reports are submitted to the workers' compensation agency, or the carrier, for further action or for use as an instrument to aid adjudication.

Comment

An increasing body of legislation is making mandatory certain examinations of the worker. As more occupational health and safety standards are produced, as workers' compensation schemes become more complex and as more disability retirement programs evolve, more physicians will be doing more examinations, as required by law. The increase in a repetitive professional activity usually conjures up timesaving forms and check-off lists. From experience, one pleads for the use of narrative reports, for they provide greater detail, the opportunity for objective comment, and a true expression of the physician regarding the feeling and tone of the examination experience.

No comment is offered relative to the worker's

motivation toward multiple or sequential examinations. This area is a separate enterprise usually developed under the rubric of health education or patient education, and normally is a concomitant of any industrial, in-plant evaluation program. For success, there must be a positive view toward such periodic determinations of health status.

Further, implicit in this discussion is the need for honesty in reporting, for only then do physical examination results assume strength and credence. Misstatements and approval of a substandard worker as fit to undertake a task which places innumerable persons at life-and-death risk is unconscionable and only does society a disservice.

Last, it is hoped that all examinations be conducted in light of their singular preventive medicine worth, and not merely a form of instrumented lip service to comply with regulations born of fine intention.

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Perils of Needle Tracheotomy

NEEDLE TRACHEOTOMY is not entirely without difficulty in that there is a small artery, a branch of the inferior thyroid, the cricothyroid, which can be pierced by the needle. Although this is a life-saving procedure and is a good alternative, it is important to remember that artery. I had one patient who lost about six units of blood after "just" a transcricothyroid aspiration of subglottic secretions for bacteriological examination. So, it is something to keep in mind.

—AUDIENCE COMMENT

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 10, No. 7, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles in other journals which they consider to be important. The editors believe these titles together with a brief assessment of the articles are worth publishing for the information of our readers.*

Treatment Planning for Children: A Complete Child Psychiatry Outline

Haslett NR

Psychiatry Digest
16:11, 21-34, Nov 1977

DISCIPLINE: Psychiatry

READABILITY: Very good

A comprehensively informative account of the work of child psychiatrists, an area unfamiliar and mysterious to most physicians.

—HELEN TAUSEND, MD
Los Angeles

Review Article: Severe Radiation Injuries of the Lung

Rosewit B, White DC

American Journal of Roentgenology
129:127-136, Jul 1977

DISCIPLINE: All

READABILITY: Very good

An excellent review article on the clinical aspects and histopathology of severe radiation injuries of the lung by authors who have had a long-standing interest in the subject. The paper is directed to physicians who are not familiar with this uncommon problem but may encounter it in patients referred for thoracic irradiation.

—MELVIN M. FIGLEY, MD
Seattle

1977 Henry H. Janeway Lecture: Fundamental Mechanisms in Combined Modality of Cancer

Kaplan HS

American Journal of Roentgenology
129:383-393, Sep 1977

DISCIPLINE: All

READABILITY: Very good

Dr. Kaplan's Janeway Lecture is a model of careful organization and textural brevity describing the many interrelated aspects of combined therapy of neoplasms with radiation, drugs, hyperthermia and surgical operation. It is a very readable, up-to-date review by one of the world's authorities and should be of interest to a wide segment of practicing physicians.

—MELVIN M. FIGLEY, MD
Seattle

Angiodysplasia of the Right Colon: A Case of Gastrointestinal Bleeding

Baum S, Athanasoulis CA, Waltman AC, et al

American Journal of Roentgenology
129:789-794, Nov 1977

This beautifully illustrated article describes the occult vascular malformations that have rather recently been found to be important causes of gastrointestinal bleeding in adults. The text is very lucid and the article should be of interest to physicians and surgeons who may be unaware of this entity.

—MELVIN M. FIGLEY, MD
Seattle

Cesarean Section and Maternal Mortality in Rhode Island

Evrard JR, Gold EM

Obstetrics and Gynecology
50:594-597, Nov 1977

DISCIPLINES: Obstetrics, Gynecology, Family Practice

READABILITY: Very good

This was an 11-year study, from January 1965 through December 1975, of cesarean sections in Rhode Island prompted by the rapid rise in the section rate. The uncorrected data showed a risk factor 26 timees greater for cesarean sections than for vaginal delivery. The authors do, however, recognize the need for expanding the indications for sections, but recommend continued close surveillance.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Management of Uterine Perforation Following Elective Abortion

Friedman SM, Wulff G

Obstetrics and Gynecology
50:647-650, Dec 1977

DISCIPLINES: Obstetrics, Gynecology, Surgery, Family Practice

READABILITY: Very good

This is a "how to" article It describes measures taken at Washington University School of Medicine (St. Louis) for prevention of perforations, as well as the abortion technique they use and the procedures they follow when perforation occurs.

—E. R. W. FOX, MD
Coeur d'Alene, ID

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

DIAGNOSTIC BRONCHOSCOPY—An Introduction—Third Edition—Peter Stradling, MD(Lond), FRCP, FRPS, Director of the Chest Clinic and Senior Lecturer in Respiratory Diseases, Royal Postgraduate Medical School, Hammersmith Hospital, London. Longman Inc., 19 West 44th Street, New York City (10036), 1976. 150 pages, $35.00.

This brief (150-page) text on bronchoscopic technique is superbly illustrated with 168 excellent color plates of remarkable photographic quality, each showing different regions and a wide variety of pathological abnormalities of the tracheobronchial tree. Each plate is accompanied by an explanatory labeled diagram plus the location of the bronchoscopic view in the tracheo-bronchial anatomy. These beautiful photographs alone are well worth the price of the book and provide great educational value both to the inexperienced and to veteran bronchoscopists.

Additional black and white illustrations clearly show the technique of instrumentation and should be very useful in teaching. The narrative text and labeling of the illustrations is clear, concise and easily read.

The author deals with indications and manipulations of both the rigid and fiberoptic bronchoscope. He describes normal bronchial anatomy and dwells on the changes occurring with inflammatory disease, displacement and tumors.

This treatise is the best and most useful teaching reference for would-be bronchoscopists. It deserves a position in the library, if not even the operating room, of every thoracic or endoscopic service.

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RENAL AND ELECTROLYTE DISORDERS—Edited by Robert W. Schrier, MD, Professor of Medicine, University of Colorado School of Medicine, Denver; with 12 contributing authors. Little, Brown and Company, Medical Division, 34 Beacon Street, Boston (02106), 1976. 500 pages, $16.50.

Robert Schrier and his contributing authors have written a good text of nephrology in less than 500 pages. Most chapters can be read by physician-in-training or expert and appreciated by both at their own level of expertise. Notable exceptions to this statement would be the chapters on calcium and magnesium. Here considerable knowledge of nonrenal disease is necessary to really understand the concise remarks regarding abnormalities in the metabolism of these two electrolytes.

Most of the material in this book is well organized. However, the initial chapters dealing with water metabolism, sodium excretion, edematous states and diuretics could present problems for the renal physiology novice. The near total separation of water handling and sodium excretion into two chapters makes urinary concentration and dilution even more difficult to understand than usual. Cross-referencing in these chapters is helpful in solving part of this problem. The chapters on water metabolism and sodium excretion are weakened by the addition of pathophysiologic discussions in both chapters of entities such as congestive heart failure. The salt and water abnormalities in such clinical states would be better discussed at one time in a separate section of the book. Similarly the section on diuretics would be stronger if more attention was paid to changes in water metabolism due to diuretic therapy.

The text presents an excellent mixture of theoretical and practical information. The chapters on acid base disturbances contain useful differential diagnostic lists and rules of thumb for assessing the severity of the disturbances and their compensatory mechanisms.

Most nephrologists care for patients with urinary tract infections and kidney stones. This book, like most other texts including those of much greater length, does not deal with these two areas. Though the pathogenesis of stone formation is far from clear and the importance of urinary tract infection to renal failure uncertain in the persons without obstruction, these topics should be discussed.

The text contains excellent references including some from the year of publication. Internally, the work is well cross-referenced and has a usable index. The book would be organizationally easier to follow if a lettered and numbered outline system had been used instead of utilizing three or four differing sizes of type for headings.

This book is an excellent collection of important topic discussions, rendered briefly in a practical and theoretical fashion. It is as good as any other concise renal text available to the student and clinician.

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University of California Medical Center
San Diego

* * *

MOTOR DISORDERS OF THE ESOPHAGUS—Robert D. Henderson, MB, FRCS(C), Associate Professor of Surgery, University of Toronto; Chief of Surgery, Women's College Hospital; Consultant Surgeon, Toronto General Hospital and Princess Margaret Hospital, Toronto. The Williams & Wilkins Company, Baltimore (21202), 1976. 231 pages, $22.50.

This 223-page monograph has many strong points and some weak ones. The strengths lie in its excellent discussions of clinical findings and treatment of common conditions producing motor disorders of the esophagus. The author's wealth of experience with these conditions can be readily appreciated.

The book contains a number of excellent illustrations: photographs, tracings, drawings and radiographs. The references are representative of the field and excellent, but few extend beyond 1970. Only a very few refer to articles published in 1974 and only an exceptional reference is made to an article published in 1975. This explains why the author is still making a great point of the role of gastrin in the control of the tone of the lower esophageal sphincter. This attractive hypothesis has recently been found not to be tenable.

The classification of hiatus hernias as type I, type II and type III, according to the location of the cardia, whether in the chest or abdomen, is also not very meaningful today because it can be shown at fluoroscopy that most of the cases of type II hiatus hernias in this classification at times present as type III if more intra-abdominal pressure is applied.

The book is at its best in the description of surgical procedures used to correct various disorders. The discussion of the respective merits of the various surgical procedures is incisive and logical. It shows not only great clinical experience but also the sound judgment of a leader in the field.

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CURRENT CONCEPTS IN RADIOLOGY—Volume Three—Edited by E. James Potchen, MD., Chairman, Department of Radiology, Michigan State University, East Lansing, Michigan, The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, Missouri (64103), 1977. 453 pages, $39.50.

The editor has assembled a group of distinguished contributors in this third volume in the series of *Current Concepts in Radiology*. Besides chapters with timely discussion of standard radiographic techniques, emphasis is given in the majority of chapters to the rapidly advancing technology of computed tomography and to progress in nuclear radiology. The selected topics included in this volume are: (1) information systems in department operations, (2) image quality of computed tomography, (3) computed tomography and its application to nuclear medical imaging, (4) computed tomography of the abdomen and aorta, (5) alternative display formats for computed tomography (CT) data, (6) radiologic detection of breast cancer, (7) some metabolic considerations in bone disease, (8) bone imaging, (9) comparative radiology: dysplasias of the canine forelimb, (10) radiologic diagnosis of pleural effusions, (11) linear shadows in chest radiographs, (12) radionuclide imaging of the myocardium, (13) thrombus detection, (14) electrocoagulation of small lung tumors, (15) some basic considerations of cerebrospinal fluid physiology as reflected by CSF imaging studies, (16) radionuclide liver imaging, and (17) evaluation of diagnostic screening tests: a case study in hypertension.

The first chapter deals with the comparison of automated versus manual informational systems. It covers the subject completely, including cost analysis. The four chapters on computed tomography are of particular and timely interests to diagnostic radiologists trying to keep up with recent advances.

The editor has succeeded in his attempt to provide a bridge between the current journal publications and the more formal textbooks in the field. This volume is recommended reading to diagnostic radiologists and physicians working in the field of nuclear medicine.

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Clinical Professor of Radiology
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TEXTBOOK OF PHYSIOLOGY AND BIOCHEMISTRY—Ninth Edition—George H. Bell, BSc, MD (Glasg), FRSE, Professor of Physiology in the University of Dundee; Honorary Fellow of the Acçadèmia Anatomico-Chirurgica of Perugia; Donald Emslie-Smith, MD(Aberd), FRCP, FRCP(Edin), Reader in Medicine in the University of Dundee; Honorary Consultant Physician, the Royal Infirmary and Ninewells Hospital, Dundee; and Colin R. Paterson, DM, BSc(Oxon), MRCPath, Senior Lecturer in Biochemical Medicine in the University of Dundee; Honorary Consultant to the Tayside Area Health Board. Churchill Livingstone—Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 733 pages, $20.00 (paperback).

This is the ninth edition of a book that first appeared in 1950 and has become a standard text in the basic medical sciences. In its early editions, it had a hard cover and was a weighty medical tome. The current edition is in paperback and has only 697 pages, exclusive of the index. Despite this apparent reduction in size, it still contains a good deal of information because the pages are large and double columned.

I must admit that I have long admired this book for its illustrations, and some years ago, I borrowed several of them for my own textbook of physiology. The present edition continues the tradition of excellent, simple and illustrative line drawings. It also contains some very good photographs, but unfortunately the reproduction of photographs in the present edition is of poor quality throughout the book, and much of the detail is lost.

The book is unique among the major basic science texts in that it combines coverage of biochemistry and physiology. The result, not surprisingly, is that both subjects are slighted to some degree. Most of the biochemistry is physiological chemistry and the coverage of some aspects of modern biochemistry is skimpy. On the physiological side, the coverage of the nervous system and the endocrine system is somewhat cursory. However, the book is generally well written, and it provides a good if somewhat superficial coverage of medically relevant aspects of biochemistry and physiology.

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* * *

A TEXTBOOK OF EPILEPSY—Edited by John Laidlaw, FRCP (Edin), Senior Physician to Chalfont Centre for Epilepsy; Physician-in-charge of the National Hospitals—Chalfont Centre for Epilepsy and Honorary Consultant to the National Hospital; and Alan Richens, PhD, MRCP, Senior Lecturer in Clinical Pharmacology, St. Bartholomew's Hospital, London; Honorary Consultant, The National Hospitals—Chalfont Centre for Epilepsy and Honorary Lecurer, Institute of Neurology, The National Hospital, London. Churchill Livingstone—Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 389 pages, $39.50.

This multiple-authored British text on epilepsy edited by Laidlaw and Richens joins a number of other good books on the subject that have been published in recent years. In general the book follows traditional lines, containing chapters on the neurology of epilepsy, fits in childhood, electroencephalography, the psychiatric aspects of epilepsy, clinical pharmacology and medical treatment of epilepsy, neuroradiology, neurosurgical treatment, and the neuropathology and pathophysiology of epilepsy. The chapters entitled "People With Epilepsy—The Burden of Epilepsy" and "People With Epilepsy—Living With Epilepsy" differ refreshingly from those found in the average neurological text. These chapters explore and discuss some of the vital sociomedical issues created by epilepsy, using actual case histories to effectively illustrate the point.

The two chapters dealing with the neurology of epilepsy and the choice of anticonvulsant medication which are written from an American point of view provide an interesting contrast to the otherwise all-English production. It is worthy of note, for instance, that certain therapies considered outmoded in the United States continue to be used in England, for example, intramuscular administration of paraldehyde for status epilepticus, a treatment generally abandoned in America because of the potentially serious necrotoxic effects of the drug. On the other hand, the book discusses the use of such new and effective anticonvulsant drugs as sodium valproate, which has not as yet been released for general use in this country. The volume contains a great deal of useful, well written, and well referenced information. It lives up to the claims made by its authors: "intelligible and of considerable value to any intelligent, educated, nonmedical person with a particular interest in epilepsy" and that physicians "in other disciplines should be able to understand fully what they are reading." Although the book should be useful to any number of professionals who deal with patients afflicted with epilepsy, from the family practitioner to the social worker, the book is probably more appropriate for British professionals operating in a somewhat different sociomedical climate and health care delivery system from those in the United States.

PIERRE M. DREYFUS, MD
Professor and Chairman
Department of Neurology
University of California, Davis

in memoriam

Ball, Dexter R., Santa Ana. Died January 4, 1978 in Santa Ana, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1921. Licensed in California in 1921. Dr. Ball was a retired member of the Orange County Medical Association.

Bennett, DeWitt Clinton, jr., San Gabriel. Died August 26, 1977 in San Gabriel of ruptured esophageal varices, aged 59. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1942. Licensed in California in 1942. MD degree from California College of Medicine, 1962. Dr. Bennett was a member of the Los Angeles County Medical Association.

Blanche, Donald W., Los Angeles. Died October 7, 1977 in Pasadena of amyloidosis, aged 71. Graduate of the University of Oregon Medical School, Portland, 1932. Licensed in California in 1932. Dr. Blanche was a retired member of the Los Angeles County Medical Association.

Brandes, Leo, Los Angeles. Died November 24, 1977 in Los Angeles of lung cancer, aged 81. Graduate of Rush Medical College, Chicago, 1922, Licensed in California in 1922. Dr. Brandes was a retired member of the Los Angeles County Medical Association.

Cohen, Peter, San Francisco. Died December 20, 1977 in San Francisco of heart disease, aged 71. Graduate of the University of Rochester School of Medicine and Dentistry, 1933. Licensed in California in 1934. Dr. Cohen was a retired member of the San Francisco Medical Society.

Cole, Leon Rykoff, Beverly Hills. Died May 7, 1977 in Los Angeles, aged 54. Graduate of Columbia University College of Physicians and Surgeons, New York, 1946. Licensed in California in 1948. Dr. Cole was a member of the Los Angeles County Medical Association.

Davis, Gerald E., Redwood City. Died January 8, 1978 in Redwood City, aged 72. Graduate of Columbia University College of Physicians and Surgeons, New York, 1930. Licensed in California in 1935. Dr. Davis was a retired member of the San Mateo County Medical Society.

DeWeese, Roger Erie, jr., San Francisco. Died December 3, 1977 in San Francisco, aged 63. Graduate of the University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Dr. DeWeese was an associate member of the San Francisco Medical Society.

Ferguson, Ralph A., Los Angeles. Died August 29, 1977 in Duarte of carcinoma, aged 75. Graduate of Rush Medical College, Chicago, 1930. Licensed in California in 1930. Dr. Ferguson was a member of the Los Angeles County Medical Association.

Gairdner, Thomas M., Sherman Oaks. Died September 12, 1977 in Newport Beach of metastatic cancer, aged 73. Graduate of the University of Nebraska College of Medicine, Omaha, 1929. Licensed in California in 1944. Dr. Gairdner was a member of the Los Angeles County Medical Association.

Gocke, John A., Los Angeles. Died in November 1977 of heart disease, aged 73. Graduate of St. Louis University School of Medicine, 1931. Licensed in California in 1932. Dr. Gocke was a member of the Los Angeles County Medical Association.

Gonzalez, Dario P., Los Angeles. Died November 6, 1977 in Pasadena of cancer, aged 51. Graduate of Universidad Nacional Facultad de Medicina, Mexico City, 1952. Licensed in California in 1957. Dr. Gonzalez was a member of the Los Angeles County Medical Association.

Greganti, Frank Paul, Glendale. Died November 8, 1977 in Pasadena of heart disease, aged 44. Graduate of Harvard Medical School, Boston, 1957. Licensed in California in 1961. Dr. Greganti was a member of the Los Angeles County Medical Association.

Gregorius, H. Harvey, Burbank. Died December 28, 1977 in North Hollywood of heart disease, aged 62. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1944. Licensed in California in 1944. Dr. Gregorius was a member of the Los Angeles County Medical Association.

Hall, William W., Bakersfield. Died January 6, 1978 in San Diego of natural causes, aged 85. Graduate of the University of Minnesota Medical School, Minneapolis, 1918. Licensed in California in 1946. Dr. Hall was a retired member of the Kern County Medical Society.

Husser, George D., Richmond. Died December 27, 1977 in San Pablo of heart disease, aged 67. Graduate of the University of California Medical School, Berkeley-San Francisco, 1937. Licensed in California in 1937. Dr. Husser was a retired member of the Alameda-Contra Costa Medical Association.

Johnston, S. Theron, San Diego. Died November 24, 1977 in San Diego, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1918. Licensed in California in 1918. Dr. Johnston was a retired member of the Orange County Medical Association.

Kazmi, Syed, Chowchilla. Died December 13, 1977 in Chowchilla, aged 33. Graduate of King Edward Medical College, Lahore, Punjab, West Pakistan, 1969. Licensed in California in 1975. Dr. Kazmi was a member of the Merced-Mariposa Medical Society.

KIRBY, JOHN M., Bakersfield. Died December 12, 1977 in Bakersfield, aged 85. Graduate of Emory University School of Medicine, Atlanta, 1922. Licensed in California in 1924. Dr. Kirby was a member of the Kern County Medical Society.

KISTLER, LEWIS MAXWELL, North Hollywood. Died August 31, 1977 in Burbank of cancer, aged 62. Graduate of the University of Southern California School of Medicine, Los Angeles, 1940. Licensed in California in 1940. Dr. Kistler was a member of the Los Angeles County Medical Association.

KROLL, FREDERICK WALTER, San Francisco. Died December 15, 1977 in San Francisco, aged 92. Graduate of Cooper Medical College, San Francisco, 1912. Licensed in California in 1912. Dr. Kroll was a retired member of the San Francisco Medical Society.

LEE, DAULTON BRADLEY, Redondo Beach. Died August 5, 1977 in Palos Verdes Estates of cancer, aged 56. Graduate of the University of Southern California School of Medicine, Los Angeles, 1951. Licensed in California in 1951. Dr. Lee was a member of the Los Angeles County Medical Association.

MCCRACKEN, JACOB H., San Pedro. Died September 19, 1977 of cerebral thrombosis, aged 76. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1926. Licensed in California in 1929. Dr. McCracken was a member of the Los Angeles County Medical Association.

MOHUN, CHARLES C., San Francisco. Died December 2, 1977, aged 75. Graduate of St. Louis University School of Medicine, 1926. Licensed in California in 1927. Dr. Mohun was a member of the San Francisco Medical Society.

MOODY, E. EARL, Los Angeles. Died in October 1977, aged 88. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, 1917. Licensed in California in 1917. Dr. Moody was a member of the Los Angeles County Medical Association.

MULLIGAN, HAROLD R., Corona del Mar. Died March 8, 1977 of heart disease, aged 86. Graduate of the University of Nebraska College of Medicine, Omaha, 1920. Licensed in California in 1924. Dr. Mulligan was a member of the Los Angeles County Medical Association.

PIES, MORRIS, Encino. Died June 29, 1977 in Tarzana of heart disease, aged 65. Graduate of Syracuse University College of Medicine, 1940. Licensed in California in 1944. Dr. Pies was a member of the Los Angeles County Medical Association.

RARICK, IVAN H., SR., North Highlands. Died December 11, 1977 in Sacramento, aged 69. Graduate of State University of Iowa College of Medicine, Iowa City, 1933. Licensed in California in 1946. Dr. Rarick was a retired member of the Sacramento County Medical Society.

ROTTSCHAFER, GERALD, San Diego. Died December 18, 1977, aged 66. Graduate of the University of Michigan Medical School, Ann Arbor, 1940. Licensed in California in 1948. Dr. Rottschafer was a member of the San Diego County Medical Society.

RUSCHIN, LOUIS JOHN, Santa Cruz. Died January 9, 1978 in Santa Cruz, aged 65. Graduate of McGill University Faculty of Medicine, Montreal, 1939. Licensed in California in 1940. Dr. Ruschin was a member of the Santa Clara County Medical Society.

SCHUMACHER, IRWIN C., San Francisco. Died November 26, 1977 in San Francisco, aged 84. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1919. Licensed in California in 1921. Dr. Schumacher was a retired member of the San Francisco Medical Society.

SHULTZ, ELLWOOD, Los Angeles. Died October 22, 1977 in Los Angeles of metastatic cancer, aged 75. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1930. Dr. Shultz was a member of the Los Angeles County Medical Association.

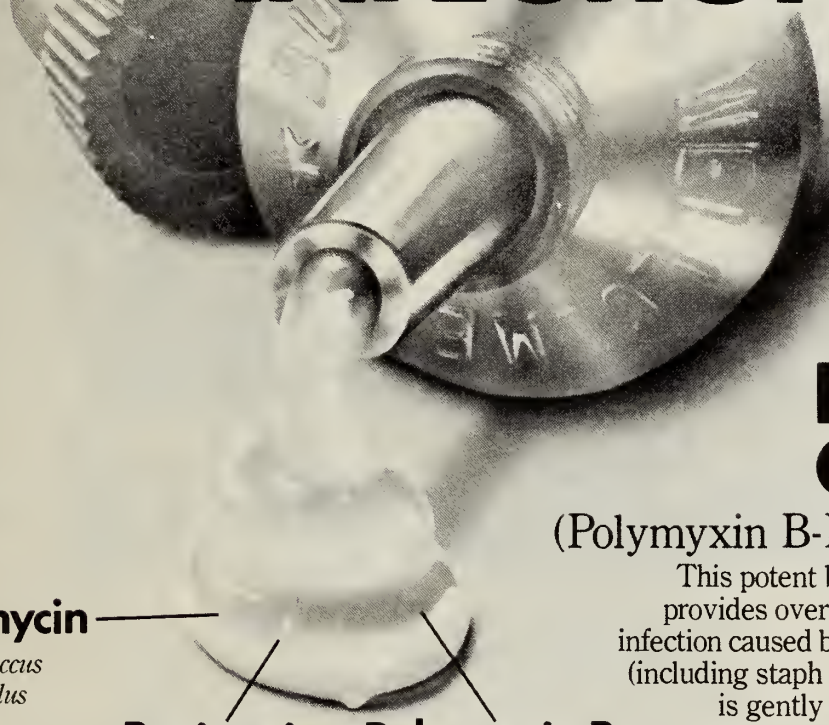
SPRONG, DAVID H., JR., Santa Monica. Died January 9, 1978 of heart disease, aged 73. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1932. Licensed in California in 1940. Dr. Sprong was a retired member of the Los Angeles County Medical Association.

SYMAN, LEO W., Laguna Hills. Died March 1, 1977 of myocardial infarction, aged 74. Graduate of the University of Colorado School of Medicine, Denver, 1926. Licensed in California in 1927. Dr. Syman was a retired member of the Los Angeles County Medical Association.

TAUBERT, RALPH T., Redlands. Died December 30, 1977, aged 53. Graduate of the University of Michigan Medical School, Ann Arbor, 1949. Licensed in California in 1955. Dr. Taubert was a member of the San Bernardino County Medical Society.

WILSON, BYRON KENT, Woodland. Died December 30, 1977 in Woodland, aged 56. Graduate of the University of Utah College of Medicine, Salt Lake City, 1951. Licensed in California in 1958. Dr. Wilson was a member of the Yolo County Medical Society.

THREE-IN-ONE THERAPY AGAINST TOPICAL INFECTION



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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section.).

Complete literature available on request from Professional Services Dept. PML.

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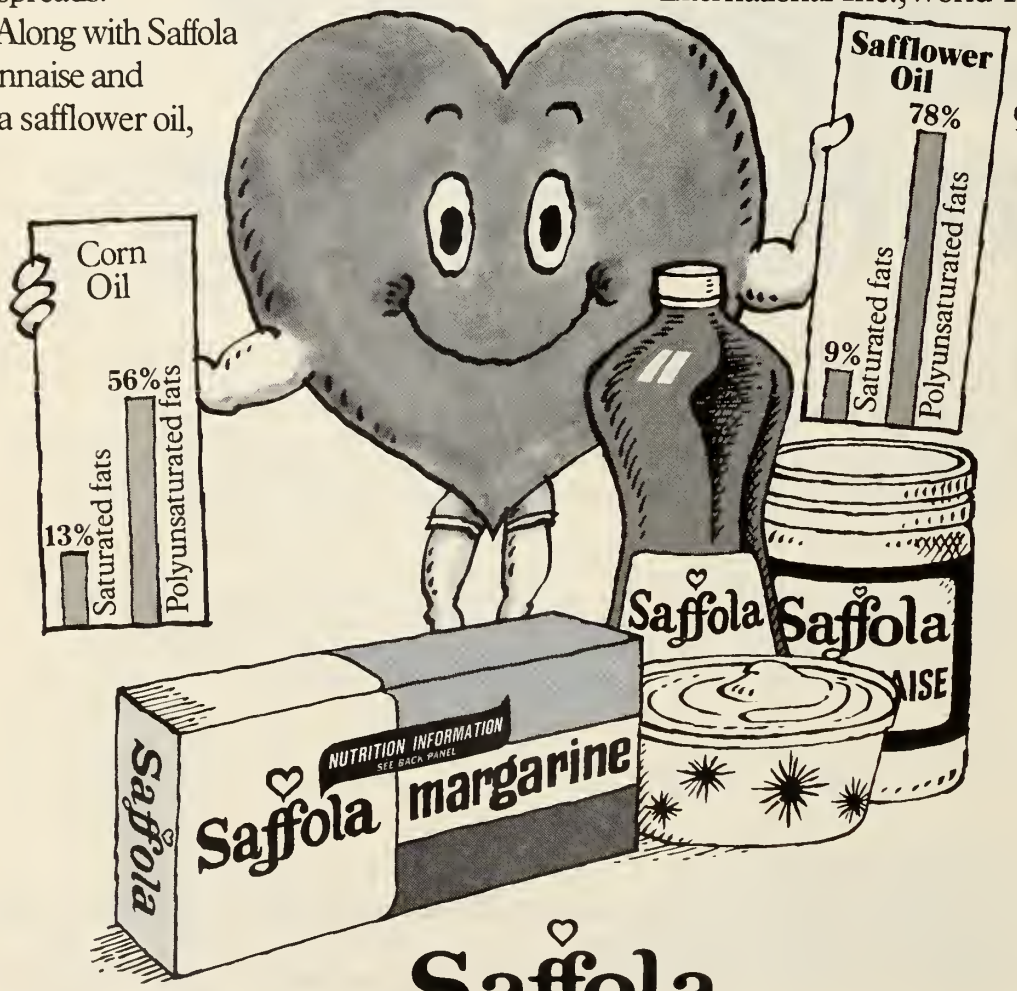

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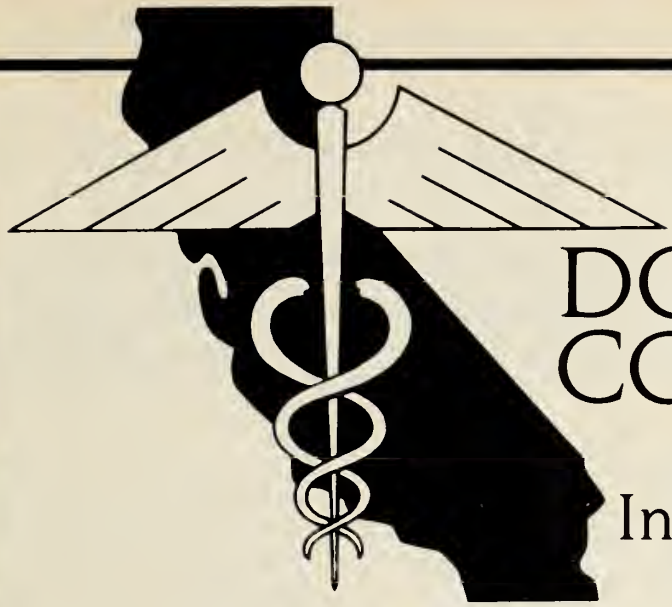

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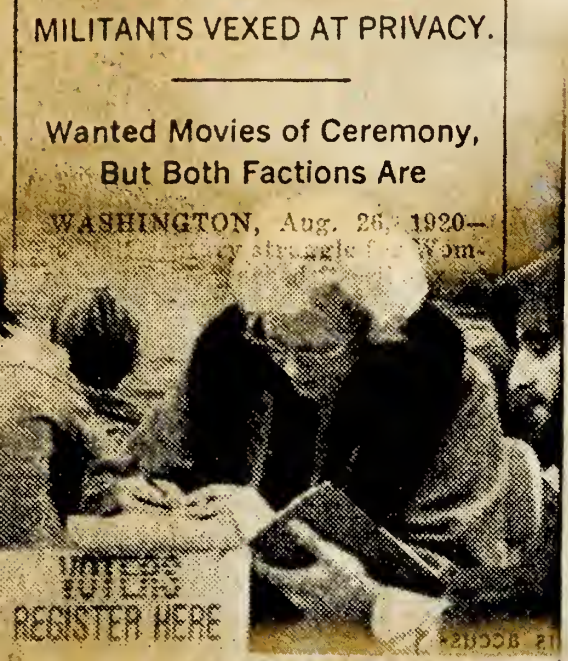
WASHINGTON, Aug. 26, 1920—[illegible] Wom-



Social Security Bill Is Signed, Gives Pensions to Aged, Job

Roosevelt Approves Message Intended to Benefit 30,0 Persons When States Adopt Cooperating Laws—He the Measure 'Cornerstone' of His Economic Progr

WASHINGTON, Aug. 1 The Social Security Bill, a broad program of unem insurance and old age and counted upon to ben 20,000,000 persons, becam day when it was signed dent Roosevelt in the pr those chiefly responsible ting it through Co[illegible]s.

Mr. Roosevelt cal[illegible] "the cor[illegible]erstone [illegible] whi[illegible] is [illegible]eing [illegible] me[illegible]s c[illegible]ple[illegible] ri[illegible]

SENATE APPROVES 18-YEAR OLD VOTE IN ALL ELECTIONS

Amendment to Constitution is Sent to House, Where Passage is Expected

WASHINGTON, March 10, 1971—The Senate approved today, 94 to 0, and sen[illegible]

TRUMAN CLOSES [illegible]ITED NATIONS CONFEREN[illegible] [illegible]ITH PLEA TO TRANSLATE CHARTER INTO DEEDS

NEW WORLD HOPE

President Hails 'Great Instrument of Peace,' Insists It Be Used

HISTORIC LANDMARK

Meeting Gives Standing Ovation as Executive Pictures Peace Gain

"If we fail to use it," he declared to the solemn final meeting of the delegates, 'we shall betray all of those who have died in order that we might meet here in freedom and safety to create it.'

"If we seek to use it selfishly—for the advantage of any one nation or any small group of nations—we shall be equally guilty of that betrayal."

Fervent Interpolation

The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session the President accompanied the

[illegible]OL[illegible] [illegible]IGN[illegible] the Dra[illegible] Ends No[illegible]

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Army that

PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

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SCOPE: This is a general course in diving medicine and is designed to acquaint physicians with the basic medical problems in diving. It will be limited to approximately 40 students. Topics include the physics and physiology of diving, physical examination of prospective divers, diagnosis and treatment of diving diseases and accidents, and an introduction to hyperbaric medicine. Instruction is carried out through lectures, demonstrations and optional training films. A double lock recompression chamber conventionally used for treatment of decompression sickness will be provided for demonstrations, class instruction and laboratory work. There will be ample time for informal discussions, with the faculty and for certified divers to enjoy the excellent local diving. Qualified applicants will be accepted on a first-come first served basis until the limited quota is filled. Early application is desirable.

ACCREDITION: This course has been approved for Category 1 (25 Hours) accreditation for the American Medical Association's Physicians Recognition Award.

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Tell it to the FDA

Saturday, March 18, 1978

2:00 to 5:00 p.m. • Masonic Temple Auditorium

The Food and Drug Administration is genuinely interested in establishing communication with practicing physicians. At the CMA Annual Session, high-level representatives of the FDA will conduct an open meeting with interested members of the CMA to foster this communication. Physicians are at the interface where the actions or interactions of the FDA have an effect upon patient care This is an opportunity to "Tell it to the FDA."

Tablets
Percocet®-5 (C II)

DESCRIPTION Each tablet of PERCOCET®-5 contains 5mg oxycodone hydrochloride (WARNING: May be habit forming), 325mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

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November 1977 EDO 148P

FOR MODERATE TO MODERATELY SEVERE PAIN

Acetaminophen with the narcotic difference

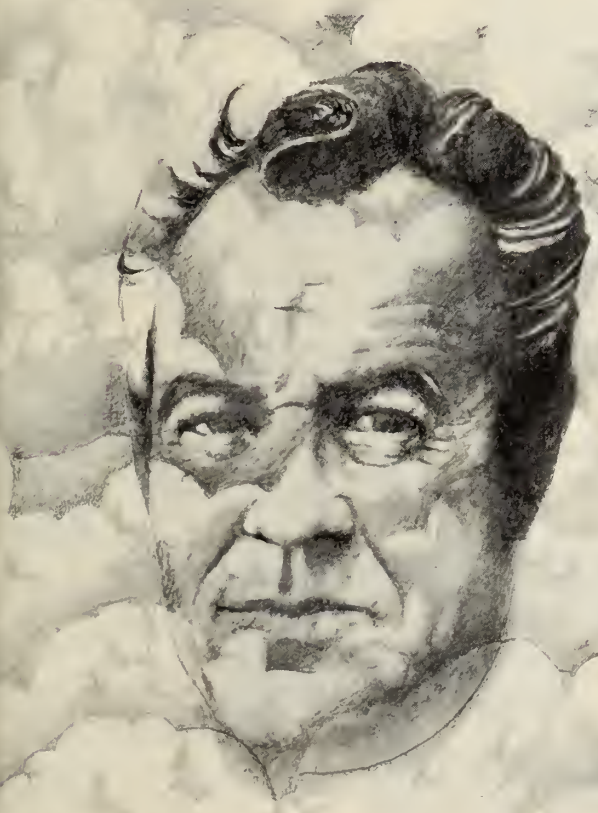
Reliable oral narcotic analgesia...

The narcotic component in PERCOCET®-5 is oxycodone, which is readily absorbed and provides dependable oral analgesia—usually within 15 to 30 minutes. Oxycodone can produce drug dependence of the morphine type and should be prescribed with the same degree of caution appropriate to the use of other narcotic-containing medications.

...aspirin free

Acetaminophen is a non-narcotic analgesic widely used for aspirin-sensitive patients. Equivalent to aspirin in analgesia, it complements the pain relief provided by oxycodone.

The usual dose of PERCOCET®-5 is one tablet every six hours, providing convenience and economy for your patients. PERCOCET®-5 is ideally suited for your patients with aspirin sensitivity, with hemostatic disturbance, with peptic ulcer or on anticoagulation therapy.



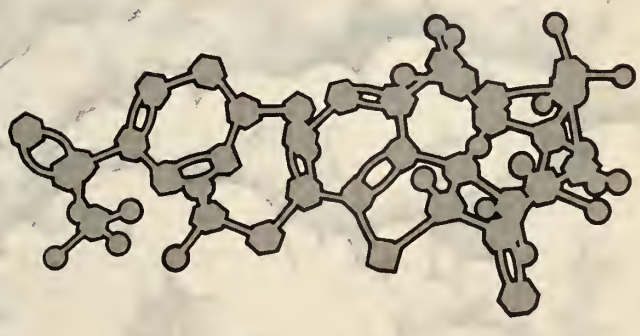
Tablets

Percocet®-5

each scored tablet contains 5 mg oxycodone HCl (WARNING: may be habit forming) and 325 mg acetaminophen

CII

When aspirin is contraindicated.



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Please see facing page for Brief Summary of prescribing information.

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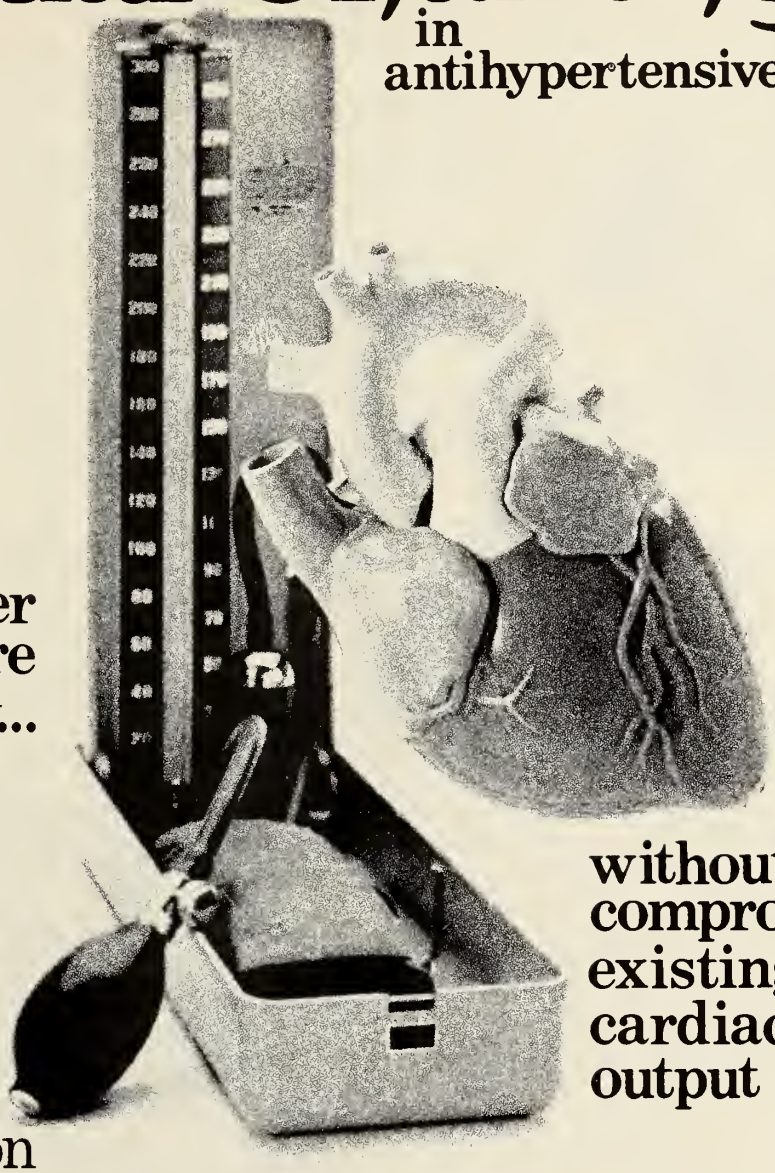
A Dual Challenge

in antihypertensive therapy



to lower blood pressure effectively...

without compromising existing cardiac output

in hypertension

TABLETS: 250 mg, 500 mg, and 125 mg

ALDOMET® (METHYLDOPA | MSD)

helps lower blood pressure effectively... usually with no direct effect on cardiac function–cardiac output is usually maintained

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.
It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

MSD
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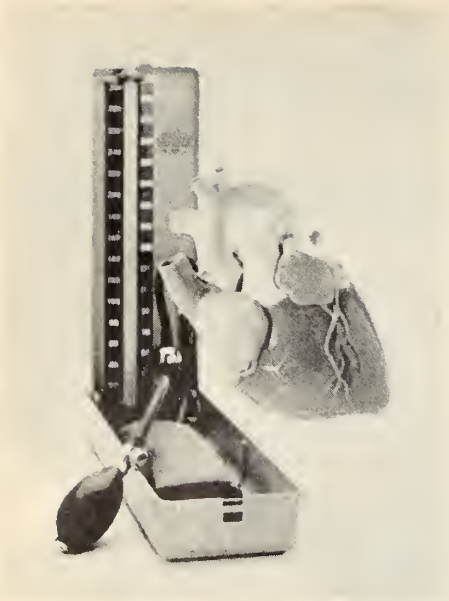

in hypertension

ALDOMET®

(METHYLDOPA|MSD)

helps lower blood pressure effectively... usually with no direct effect on cardiac function– cardiac output is usually maintained

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ASIAN MEDICAL SYSTEMS: A Comparative Study—Edited by Charles Leslie, PhD, Professor of Anthropology, New York University, New York City. University of California Press, 2223 Fulton Street, Berkeley, CA (94720), 1978. 433 pages, $16.50 (cloth), $5.95 (paperback).

CLINICAL CARDIOLOGY—Maurice Sokolow, MD, Professor of Medicine, Senior staff member, Cardiovascular Research Institute; formerly Chief of Cardiology and Program Director of the USPHS Clinical Cardiology Training Program, University of California, San Francisco; and Malcolm B. McIlroy, MD, Professor of Medicine and Senior staff member, Cardiovascular Research Institute, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 659 pages, $16.00.

CURRENT MEDICAL DIAGNOSIS & TREATMENT 1978—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine; Director of Research, Palo Alto Medical Research Foundation; Director of Laboratories, Palo Alto Medical Clinic; Milton J. Chatton, MD, Clinical Professor of Medicine, Stanford University School of Medicine: Senior Attending Physician, Santa Clara Valley Medical Center, San Jose; Research Associate, Palo Alto Medical Research Foundation; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1978. 1,098 pages, $17.00.

DIABETIC MENUS, MEALS AND RECIPES—Betty M. West—Revised and expanded by Nancy Greene Eash, MS, RD, Dietitian, Metabolic Unit, City of Hope National Medical Center, Duarte, California. Doubleday & Company, Inc., 245 Park Ave., New York City (10017), 1978. 194 pages, $7.95.

GASTROENTEROLOGY: An Integrated Course—Second Edition—Editors: Iain E. Gillespie, MD, MSc, FRCS (Ed, Eng and Glasg), Professor of Surgery, The University of Manchester; Honorary Consultant Surgeon, Manchester Royal Infirmary; and T. J. Thomson, MB, ChB, FRCP (Glasg and Lond), Consultant Physician, Gastroenterology Unit, Stobhill Hospital, Glasgow; Honorary Lecturer, Department of Materia Medica, University of Glasgow. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 288 pages, $9.95 (softbound).

HANDBOOK OF CLINICAL DRUG DATA—Fourth Edition—James E. Knoben, PharmD, MPH, Regional Pharmacy Consultant, DHEW, San Francisco; Philip O. Anderson, PharmD, Clinical Pharmacist, University of California, San Diego, School of Medicine; Arthur S. Watanabe, PharmD, Associate Director, Rocky Mountain Drug Consultation Center, Denver; with contributors: William D. Ball, PharmD, Coordinator, Clinical Pharmacy Service, University Hospitals of Cleveland, and William G. Troutman, PharmD, Associate Professsor of Pharmacy, University of New Mexico, Albuquerque. Drug Intelligence Publications, Inc., Hamilton, IL (62341), 1978. 467 pages, no price given.

HIDDEN CAUSES OF INJURY, PREVENTION AND CORRECTION, FOR RUNNING ATHLETES AND JOGGERS—John Jesse. The Athletic Press, P.O. Box 2314-D, Pasadena, CA (91105), 1978. 384 pages, $12.95.

OCCUPATIONAL DISEASES: A Syllabus of Signs and Symptoms—E. R. Plunkett, MD. The Barrett Book Company, 388 Summer Street, Stamford, Connecticut (06901), 1977. 352 pages, $22.95 plus handling.

PROGRESS IN GASTROENTEROLOGY—Volume III—Edited by George B. Jerzy Glass, MD, Dr hon c (Univ. Nancy), Professor of Medicine, New York Medical College; Consultant in Gastroenterology, Memorial Hospital for Cancer and Allied Diseases, New York City. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1977. 1,052 pages, $88.50.

RETROSPECTROSCOPE—Insights Into Medical Discovery—Julius H. Comroe, Jr., MD, Morris Herzstein Professor of Biology, Cardiovascular Research Institute, and Professor of Physics, University of California, San Francisco. The Von Gehr Press, P.O. Box 7654, Menlo Park, CA (94025), 1977. 182 pages, $5.00 (Paperback).

STROKE—Proceedings of the Ninth Pfizer International Symposium held in Edinburgh from 29-30 June 1976—Editors: F. J. Gillingham, MBE, MD(Hon), FRCS(Eng), FRCP(Edin), FRS(Edin), Professor of Surgical Neurology, University of Edinburgh; C. Mawdsley, MD, FRCP, FRCP(Edin), Head, Department of Medical Neurology, University of Edinburgh; and A. E. Williams, BSc, PhD, Senior Lecturer, Department of Medicine, Western General Hospital, University of Edinburgh, Scientist In Charge, Teaching and Research Centre, Western General Hospital. Longman Inc., 19 West 44th Street, New York City (10036), 1976. 540 pages, $27.50.

THE SATURDAY EVENING POST FIBER AND BRAN BETTER HEALTH COOKBOOK—Cory SerVaas, MD, Charlotte Turgeon and Frederic Birmingham. The Curtis Publishing Company, Inc., 1100 Waterway Blvd., Indianapolis (46202), 1977. 320 pages, $12.95.

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(Continued on Page 36)

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(Continued from Page 34)

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(Continued on Page 38)

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(Continued from Page 36)

SITUATIONS WANTED

OTOLARYNGOLOGIST—32, Military completed; California university trained in all aspects of Head and Neck, Facial Plastic and Reconstructive Surgery and Otolaryngology including Maxillofacial trauma; Seeks position in Western States, Pacific Coastal preferred. Available July 1, 1978. Write Box 5965, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PULMONARY PHYSICIAN seeks to relocate. Experienced in fiberoptic bronchoscopies, private practice and management of pulmonary function and respiratory therapy. Desires hospital-based position, private practice or combination. Available immediately. Write Box 5974, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIOLOGIST-INTERNIST, 33, university-trained in invasive and noninvasive procedures seeks group or hospital based practice. Available July 1978. Reply Box 5975, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ALLERGIST—32 years old, board certified Allergy, Immunology and Pediatrics. California licensed, presently practicing Allergy in Midwest with group. Wishes to relocate. Available July 1978. Associate or group. Box 5977, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST—Pulmonary. Univ. trained, seeks solo, group hospital based practice. Emergency room experience. Interested in primary care. Prefer Southern California but will consider other areas. Flex N.Y. N.J. Reply: Rustom Damania, 108 Oak St., Ridgewood, N.J. 07450. (201) 444-0487.

PSYCHIATRIST—Board eligible, seeks solo, group, hospital based practice. Flex N.Y. N.J. Prefer California. Reply Shireen Damania, 108 Oak St., Ridgewood, N.J. 07450. (201) 444-0487.

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ACTIVE FAMILY PRACTICE, Bishop, California. Ideal location across from City Hall, 4 blocks from hospital. No OB, no major surgery. Six figure net income. Sell or lease—excellent terms. Reason for selling, chronic illness. Building fully equipped, including x-ray. Contact—C. C. Curtis, MD, 386 W. Line St., Bishop, CA 93514.

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ANESTHESIOLOGY

March 19-23—**International Anesthesia Research Society—52nd Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: B. B. Sankey, MD, IARS, 3645 Warrensville Center Rd., Cleveland OH 44122. (216) 295-1124.

March 31-April 1—**Recent Advances and Future Directions in Respiratory Monitoring.** See Medicine, March 31-April 1.

April 16-21—**California Society of Anesthesiologists—2nd Hawaii Seminar.** Hyatt Regency Hotel, Waikiki-Honolulu. Sunday-Friday. 20 hrs. Contact: CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 6-7—**American Society of Anesthesiologists Workshop.** St. Francis Hotel, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

June 1-4—**California Society of Anesthesiologists—Annual Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401.

CANCER

March 17—**Cancer of the Lung.** California Hospital Medical Center, Los Angeles. Friday. 5 hrs. $15. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 27-31—**Cancer.** STAN. Monday-Friday. 27 hrs. $265.

May 6—**Pediatric Oncology.** PMC. Saturday

May 10—**Carcinoma of the Cervix: Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $25.

June 19-23—**Head and Neck Oncology.** UCLA. Monday-Friday.

June 29-30—**Oncology Conference.** USC at Disneyland Hotel, Anaheim. Thursday-Friday.

June 30-July 1—**International Endocurietherapy Symposium.** USC at Hotel Bonaventure, Los Angeles. Friday-Saturday. 22 hrs.

EMERGENCY MEDICINE

March 20-24—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

April 3-7—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

April 15-22—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $300.

May 8-12—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

May 8-13—**Topics in Emergency Medicine,** UCSF at Ralph K. Davies Med. Center, San Francisco. Monday-Saturday.

May 10-12—**Emergency Room Radiology.** See Radiology, May 10-12.

June 3-4—**Critical Care Monitoring.** UCLA at Airport Marina Hotel, Marina Del Rey. Saturday-Sunday.

June 10—**Plastic Surgery for Emergency Physicians.** UCI. Saturday.

June 26-30—**Trauma—Major and Minor.** USC. Monday-Friday.

July 24-28—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

August 7-11—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Islandia Hyatt House, San Diego. Monday-Friday. 40 hrs. $325.

MEDICINE

March 16-19—**Viral Hepatitis.** UCSF at Hilton Hotel, San Francisco. Thursday-Sunday. 26 hrs. $145.

March 17-18—**American College of Physicians—Nevada/Northern California Regional Meeting.** Mark Hopkins Hotel, San Francisco. Friday-Saturday. Contact: Ralph O. Walerstein, MD, FACP, 3447 Clay St., San Francisco 94118.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

March 18—**Advances in Cardiology: A Practical Approach for the Primary Physician.** UCD at Holiday Inn, Chico. Saturday. 7 hrs. $55.

March 23-25—**Immunology and Allergy Conference—2nd Annual.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

March 28-31—**Consultant's Course in Dermatology—6th Annual.** UCSF. Tuesday-Friday. 25½ hrs. $250.

March 31-April 1—**Seminar on Thrombosis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 9 hrs. $75.

March 31-April 1—**Recent Advances and Future Directions in Respiratory Monitoring.** Memorial Hospital and Medical Center, Long Beach. Friday-Saturday. 14 hrs. $150. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 1-6—**American College of Allergists—34th Annual Congress.** Hilton Hotel, Las Vegas. Saturday-Thursday. 30 hrs. $75, ACA members; $190, nonmembers. Contact: Frances P. White, ACA, 2141 14th St., Boulder, CO 80302. (303) 447-8111.

April 3-12—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 3-14—**Intensive Review of Internal Medicine.** USC. 12 days.

April 5—**Clinical Disorders of Immune Regulation.** L.A. Soc. of Internal Medicine at L.A. Co. Med. Assn. headquarters, Los Angeles. Wednesday. 1 hr. Contact: Susan McNamara, Exec. Sec., LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

April 8—**The Critically Ill Cardiac Patient.** PMS. Saturday. $90.

April 12-June 14—**Nephrology for the Practicing Internist.** UCLA. Wednesday evenings; 10 weeks.

April 14-15—**Operative Arthroscopy.** See Surgery, April 14-15.

April 15-16—**Basic Approaches to the Rheumatoid Condition.** DREW at Incline Village, Lake Tahoe. Saturday-Sunday.

April 15-22—**Chronic Obstructive Pulmonary Disease—From the Beginning to the End.** International Center for Postgraduate Medical Education at Kona Surf Hotel, Hawaii. One week. 25 hrs. Contact: Ms. Kym Westenberg, ICPME, 3969 Cuervo, Santa Barbara 93110. (805) 967-0497.

April 19-21—**Echocardiographic Solutions to Clinical Cardiovascular Problems.** American College of Cardiology and UCLA at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 19-22—**California Blood Bank System—26th Annual Meeting.** Hilton Hotel, Fresno. Wednesday-Saturday. Contact: CBBS Central Office, P.O. Box 1340, Long Beach 90801.

April 24-29—**American Academy of Neurology — Annual Meeting.** Bonaventure Hotel, Los Angeles. Monday-Saturday. $35, members; $55, nonmembers. Contact: Mr. Stanley A. Nelson, Exec. Dir., AAN, 4015 W. 65th St., Suite 302, Minneapolis, MN 55435. (612) 920-3636.

April 27—**Rehabilitation Symposium.** American Heart Assn., Greater L.A. Affiliate, at Biltmore Hotel, Los Angeles. Thursday. 6 hrs. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

April 29—**Advances in Cardiology: A Practical Approach for the Primary Physician.** UCD at Royal Bay Inn, Vallejo. Saturday. 7 hrs. $55.

May 1—**Current Problems in Neuromuscular Disease.** PMC at Hyatt on Union Square, San Francisco. Monday. 6 hrs. $95.

May 4-5—**Current Concepts in Medicine: Stroke.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 13 hrs. $200.

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May 4-7—**American Society of Internal Medicine — Annual Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. Contact: ASIM, 535 Central Tower Bldg., 703 Market St., San Francisco 94103. (415) 777-1000.

May 13—**Cardiology Update.** DREW at Bonaventure Hotel, Los Angeles. Saturday.

May 13—**Controversies in Internal Medicine—2nd Annual.** San Jose Hosp. and Health Center, Inc., at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $35. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 16—**Common Skin Problems Seen in Office Practice.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, 199 E. Webster St., Colusa 95932. (916) 458-5844.

May 19—**American Heart Association, California Affiliate—Physicians' Scientific Sessions.** Vacation Village, San Diego. Friday. Contact: Marilyn Probst, AHA, Calif. Affiliate, 805 Burlway Rd., Burlingame 94010. (415) 342-5522.

May 19—**The Child With Heart Disease: The Practitioner's Role.** See Pediatrics, May 19.

May 20—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

May 22-26—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 29-June 2—**Advances in Internal Medicine.** UCSF. Monday-Friday.

June 3—**Infectious Disease Symposium.** Kaiser Foundation Hospital, Sacramento, at Kaiser Center, Oakland. Saturday. 5 hrs. Contact: Onera Roberts, Education Office, Kaiser Foundation Hosp., 2025 Morse Ave., Sacramento 95825. (916) 486-5965.

June 10—**Advances in Cardiology: A Practical Approach for the Primary Physician.** UCD at Waystation, South Lake Tahoe. Saturday. 7 hrs. $55.

June 14—**Acute and Chronic Diarrhea.** LLU. Wednesday. 4 hrs. $25.

June 15-17—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Bahia Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 24—**Allergy for the Office Practice.** PMC Saturday.

August 25-27—**Dermatomycology.** UCSF. Friday-Sunday.

OBSTETRICS AND GYNECOLOGY

March 31-April 1—**Obstetrics/Gynecology—Annual Symposium.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Symposium Coordinator, SCPMG, 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027.

April 10-12—**Antenatal Assessment of the Fetus From Conception to Delivery.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $150.

April 13-15—**Basic Colposcopy/Ob-Gyn.** UCD at Sacramento Inn, Sacramento. Thursday-Saturday.

PEDIATRICS

March 17-19—**Combined Southern California Pediatric Postgraduate Meeting—8th Annual.** American Academy of Pediatrics, District IX, Chapter 2, at Riviera Hotel, Palm Springs. Friday-Sunday. $135, members; $150, non-members. Contact: Calif. Chapter 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 5-7—**General Pediatrics.** American Academy of Pediatrics at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 7-8—**Common Problems in Ambulatory Pediatrics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9½ hrs. $50.

April 8-13—**American Academy of Pediatrics—Spring Session.** Century Plaza Hotel, Los Angeles. Saturday-Thursday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 14-15—**Comprehensive Care of the Handicapped Child.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. $75.

May 1-5—**Pediatric Review.** USC. Monday-Friday.

May 6—**Pediatric Oncology.** See Cancer, May 6.

May 11-13—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 13-20—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 28 hrs. $300.

May 19—**The Child With Heart Disease: The Practitioner's Role.** UCD at Woodlake Inn, Sacramento. Friday. 6 hrs.

May 20-21—**Neuropediatrics.** UCLA. Saturday-Sunday. 11 hrs. $165.

May 27-29—**American Academy of Pediatrics, California Chapter I, District IX.** Hyatt House, Monterey. Saturday-Monday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

June 8-9—**Pediatric Allergy and Immunology.** USC. Thursday-Friday.

PSYCHIATRY

March 27-31—**American Orthopsychiatric Association—55th Annual Meeting.** Hilton Hotel, San Francisco. Monday-Friday. 12 hrs. Contact: Dr. Marion Langer, AOA, 1775 Broadway, New York 10019.

April 15-16—**The Nature and Management of Stress.** UCLA and UC Extension, Santa Cruz, at Monterey Conference Center, Monterey. Saturday-Sunday. 12 hrs.

April 17-19—**Stress Reduction and Self-Management Techniques.** UCLA and UC Extension, Santa Cruz, at Ahwahnee Hotel, Yosemite. Monday-Wednesday. 14 hrs. $200.

May 19-21—**Treatment of Schizophrenia.** UCSF. Friday-Sunday.

June 2-3—**Psychosocial Care of the Dying Patient.** See Of Interest To All, June 2-3.

June 26-30—**Comparative Psychotherapies.** USC. Monday-Friday.

June 30-July 1—**Human Problems: Ordinary and Extraordinary—3rd Don D. Jackson Memorial Conference.** Mental Research Institute at Sir Francis Drake Hotel, San Francisco. Friday-Saturday. Contact: Peggy Smith, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

RADIOLOGY AND PATHOLOGY

March 15—**Radiation Protection and the Safe Handling of Patients.** Memorial Hospital Medical Center, Long Beach. Wednesday. 6 hrs. $50. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 9-14—**American College of Radiology—Annual Meeting and Categorical Course.** Town and Country Hotel, San Diego. Sunday-Friday. Contact: Ms. Sheila Aubin, Meeting Manager, ACR, 20 N. Wacker Dr., Chicago, IL 60606. (312) 236-4963.

April 21-22—**Seminar and Wet Tissue Workshop.** USC. Friday-Saturday.

May 4-5—**New Concepts in Medicine: Stroke.** See Medicine, May 4-5.

May 10-12—**Emergency Room Radiology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday. 15 hrs. $160.

(Continued on Page 44)

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(Continued from Page 42)

May 12—**Radiology Symposium.** UCD at Red Lion Motor Inn, Sacramento. Friday. 7½ hrs. $50.

June 3-4—**Leo Rigler Radiology Seminar.** UCLA. Saturday-Sunday.

June 18-23—**Pathology of the Lung.** UCSD. Sunday-Friday. 50 hrs. $400.

July 30-August 5—**Ultrasound and Computed Tomography.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Saturday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

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SURGERY

March 17-18—**Ophthalmology Update V.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $225.

March 21—**Urology—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 28-April 1—**Controversial Areas in Surgery—15th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Tuesday-Saturday. 16 hrs. $230.

March 30-31—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs.

April 1-5—**Vascular Surgery—6th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

April 5-9—**American Society for Dermatologic Surgery—4th Annual Clinical and Scientific Meeting.** Vacation Village, San Diego. Wednesday-Sunday. 24 hrs. $100, members; $150, nonmembers. Contact: Mr. Robert Brown, Incentive Co., 2207 Chestnut St., Philadelphia, PA 19103.

April 7-8—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

April 12-14 — **Maxillofacial Trauma Symposium.** UCSF. Wednesday-Friday.

April 13-15—**General Surgery—Annual Course.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 14-15—**Operative Arthroscopy.** UCLA. Friday-Saturday. 12 hrs. $315.

April 15-22—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 18—**Orthopaedics—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

April 20-21—**Current Concepts of Macular Structure, Function and Disease—9th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute and UCLA at Century Plaza Hotel, Los Angeles. Thursday-Friday. $225. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

April 20-21—**Current Problems in Intensive Care: The Cardiac Surgical Patient.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 11 hrs. $125.

April 21-22—**Vitrectomy Microsurgery Workshop.** VA Hospital, San Francisco. Friday-Saturday. 15 hrs. $350.

April 28-29—**Vitrectomy Microsurgery Workshop.** See above, April 21-22.

April 29-May 6—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $275.

May 1-12—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Fred H. Linthicum, MD, Dir. of Education, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

May 4-5—**New Concepts in Medicine: Stroke.** See Medicine, May 4-5.

May 6—**Flexible Bronchofibroscopy.** PMC. Saturday. 6 hrs. $300.

May 6—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 11-12—**Office Orthopedics.** USC. Thursday-Friday.

May 18-20—**Neurosurgery.** UCSF at Sheraton Palace, San Francisco. Thursday-Saturday.

June 2-3—**Intraocular Lens Implantation Course.** Santa Monica Hospital. Friday-Saturday. $600. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

June 2-4—**Soft Tissue Surgery.** USC. Friday-Saturday.

June 9-10—**Ophthalmology Update VI.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 6 hrs. $225.

June 10—**Strabismus Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 11-15—**American Society of Colon and Rectal Surgeons—Annual Convention.** San Diego. Sunday-Thursday. Contact: Harriette Gibson, Admin. Sec., ASCRS, 615 Griswold, No. 516, Detroit, MI 48226. (313) 961-7880.

June 15-17—**Hip Course.** UCLA. Thursday-Saturday.

June 15-17—**Highlights of Ophthalmology.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday. 16 hrs. $195.

August 4-5—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

March 15-18—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Wednesday-Saturday.

March 17-22—**California Medical Association—107th Annual Session.** Fairmont Hotel, San Francisco. Friday-Wednesday. Contact: Linda Ramsey, CMA.

March 25—**Burn Care for the Non-Burn Physician.** Alta Bates Hospital, Berkeley. Saturday. Contact: Dept. of Medical Education, Alta Bates Hosp., 1 Colby Plaza, Berkeley 94705. (415) 845-7110, ext. 2055.

March 29-April 2—**Family Practice—Intensive Review.** DREW. Wednesday-Sunday.

April 2-7—**Electrophysiology.** USC at Erawan Gardens, Palm Springs. Sunday-Friday.

(Continued on Page 46)

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(Continued from Page 44)

April 4-May 23—**Problem Areas in Clinical Medicine—A Practical Approach—Series I.** Daniel Freeman Memorial Hospital, Inglewood. Tuesday evenings. 16 hrs. $120. Contact: Donald Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Memorial Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext. 3427.

April 6-8—**West Coast Counties Postgraduate Institute.** CMA at Sunset Convention Center, Carmel. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 6-9—**Basic Clinical Hypnosis—2nd Annual Workshop.** UCI and Orange Co. Society of Clinical Hypnosis at Balboa Bay Club, Newport Beach. Thursday-Sunday. 23 hrs. $275. Contact: Univ. Extension, Fee and Information Office, Rm. 102 Admin. Bldg., UCI, Irvine 92717.

April 7-8—**Family Practice Symposium—6th Annual.** Southern Calif. Permanente Medical Group at Marriott Hotel, Newport Beach. Friday-Saturay. Contact: Shirley Gach, Ed. and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4241.

April 7-8—**Annual Spring Seminar.** Providence Hospital, Oakland. Friday-Saturday. Contact: Nancy Hansen, Med. Staff and CME Coordinator, Providence Hosp., Box 23020, Oakland 94623. (415) 835-4500.

April 7-9—**Resources in Human Sexuality.** National Sex Forum; Institute for Advanced Study of Human Sexuality; and San Diego Soc. for Sex Therapy and Education at Hilton Hotel, San Diego. Friday-Sunday. 15 hrs. $110. Contact: Cont. Ed., Nat'l Sex Forum, 1523 Franklin St., San Francisco 94109. (415) 928-1133 or (213) 990-0774.

April 8-9—**Hospice Care—A New Concept for the Care of the Terminally Ill and Their Families.** UCLA. Saturday-Sunday. 14 hrs. $100.

April 12—**The Prostate.** LLU. Wednesday. 4 hrs. $25.

April 15-16—**The Nature and Management of Stress.** See Psychiatry, April 15-16.

April 16-22.—**Diving Medicine.** John A. Burns School of Medicine, Univ. of Hawaii, at King Kamehameha Hotel, Kailua-Kona, Hawaii. Sunday-Saturday. 25 hrs. $250. Contact: Hawaii Conference Services, P.O. Box 22670, Honolulu 96822. (808) 373-3045 or (808) 373-3745.

April 17-19—**Stress Reduction and Self-Management Techniques.** See Psychiatry, April 17-19.

April 18-19—**Hypertension.** USC. Tuesday-Wednesday.

April 20-21—**Health, Science and Society: Scientific Solutions and Human Problems.** UCSF at Sheraton-Palace, San Francisco. Thursday-Friday. $80.

April 22-23—**Practical Dermatology for the Primary Care Physician.** UCLA. Saturday-Sunday.

April 22-29—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 27-29—**San Joaquin Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 29-30—**Sports Medicine.** UCLA. Saturday-Sunday.

May 2-30—**Overview of Integral Medicine.** UCLA. Tuesday evenings.

May 6—**Critical Care Medicine—7th Annual Symposium.** South Coast Community Hospital, South Laguna. Saturday. Contact: Sol Sloan, MD, FACP, Dir. of Med. Ed., South Coast Community Hosp., 31872 Coast Highway, South Laguna 92677. (714) 499-1311, ext. 136.

May 12-13—**Alumni Days.** UCSF. Friday-Saturday.

May 12-14—**Resources in Human Sexuality.** National Sex Forum and Institute for Advanced Study of Human Sexuality at Towne House, Fresno. Friday-Sunday. 15 hrs. $110. Contact: Cont. Ed., Nat'l Sex Forum, 1523 Franklin St., San Francisco 94109. (415) 928-1133 or (213) 990-0774.

May 13—**Clinical Pharmacology.** STAN and Palo Alto Medical Clinic at STAN. Saturday. $15.

May 13-14—**Aging.** UCLA. Saturday-Sunday. 11 hrs. $90.

May 15-21—**Diving Medicine.** UCSF at VA Hospital, Fresno. One week.

May 19-21—**Health Aspects of Human Sexuality.** Human Sexuality Program, UCSF. Friday-Sunday. Contact: John Holland, Human Sexuality Prog., UCSF, 350 Parnassus Ave., Suite 700, San Francisco 94143. (415) 666-4787.

May 20-21—**Human Sexuality.** DREW. Saturday-Sunday.

May 21-24—**Biofeedback—5th Annual Workshop.** UCLA at Biltmore Hotel, Santa Barbara. Sunday-Wednesday.

May 21-26—**Orthopaedic Symposium for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $225.

June 2-3—**Management of Medical Problems.** PMC. Friday-Saturday. 15 hrs.

June 2-3—**Psychosocial Care of the Dying Patient.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

June 3-4—**Human Sexuality.** DREW. Saturday-Sunday.

June 7-9—**Dermatology for the Family Practitioner.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Friday. 14½ hrs. $100.

June 8-10—**Nutritional Care of the Hospitalized Patient.** UCSF. Thursday-Saturday.

June 8-10—**Development of Occupational Health and Safety Services.** PMC. Thursday-Saturday.

June 10-11—**San Diego Chapter, California Academy of Family Physicians—22nd Annual Postgraduate Symposium.** Town and Country Hotel, San Diego. Saturday-Sunday. Contact: Irene Adams, Exec. Sec., SDAFP, 4406 Alta Mira, La Mesa 92041. (714) 466-0770.

June 10-11—**Practical Infectious Diseases for the Primary Care Physician.** UCLA. Saturday-Sunday.

June 18-24—**Family Practice Refresher Course—9th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. Sunday-Saturday.

June 20—**Hypertension—Rationale for Appropriate Work-Up and Advances in Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

July 22-25—**Allergy and Clinical Immunology for Non-Allergist Physicians.** American Assn. for Clinical Immunology and Allergy at Newporter Inn, Newport Beach. Saturday-Tuesday. 26 hrs. $260. Contact: AACIA, P.O. Box 912, Omaha, NE 68101. (402) 551-0801.

August 12-23—**Annual Postgraduate Refresher Course.** USC at Hawaii. 12 days.

August 13-18—**Family Practice Refresher Course—6th Annual.** UCD at Del Monte Hyatt House, Monterey. Saturday-Thursday. 30 hrs. $225.

Audio-Digest Foundation. A nonprofit educational subsidiary of the California Medical Association. Twice-a-month tape-recorded summaries of leading national meetings. Services by subscription in: Anesthesiology, Family Practice, Internal Medicine, Obstetrics/Gynecology, Ophthalmology, Otorhinolaryngology, Pediatrics, Psychiatry, Surgery. ($90.00 per year for 24 one-hour cassettes or reels.) New catalog of lectures and panel discussions in all areas of medical practice also available, as well as cassette album condensations of the following 1977 specialty meetings: postgraduate courses from the annual meeting of the American Psychiatric Assn., workshops from the annual meeting of the American College of Physicians, and postgraduate courses from the annual sessions of the American College of Obstetricians and Gynecologists. For further information on subscriptions, catalogs and special courses, contact Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

Health Research Group of the American Institutes for Research. A not-for-profit research corp. CME research project seeks physician input. Physicians in general or family practice in non-urban areas of Calif. may be contacted to participate in a major research project on development of a continuing medical education system for doctors in office practice. Project will offer, without charge, up to 30 hrs. Category I credit in return for trying out and critiquing a newly developed set of instructional materials. These materials, entitled "Management of Adult Asthma: for General and Family Physicians," and the delivery system to be tried out were developed by the Health Research Group of the American Institutes for Research under contract to the National Heart, Lung, and Blood Insitute/National Institutes of Health. Contact: Muriel H. Bagshaw, MD, Project Dir., Health Research Group, American Institutes for Research, P.O. Box 1113, Palo Alto 94302. (415) 493-3550.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213. Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OPHTHALMOLOGY

March 17-18—**The Oregon Academy of Ophthalmology Annual Convention.** Sheraton Hotel, Lloyd Center, Portland. Contact: Rebecca Tarshis, Executive Secretary Oregon Academy of Ophthalmology, 918 NE 44th Ave., Portland 97213.

PEDIATRICS

March 15-18—**North Pacific Pediatric Society Annual Meeting.** Benson Hotel, Portland. Contact: Robert Hauck, MD, 2033 Sixth Ave., Suite 900, Seattle, WA 98121.

April 5—**Circuit Course Program on Advances in Pediatrics.** St. Elizabeth Community Hospital, Baker. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

March 31-April 1—**Oregon Heart Association Annual Meeting.** Red Lion, Portland. Contact: Oregon Heart Association, 1500 SW 12th, Portland 97205.

April 12—**Environmental Factors in Human Health.** Withycombe Hall, Oregon State University, Corvallis. Contact: Robert Phillips, Admin. Services, A. 600, Oregon State University, Corvallis 97330.

April 27—**Circuit Course Program on Disorders of the Lower G.I. Tract.** Recreation Cafe, The Dalles. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

March 16-17—**Internal Medicine.** Thursday-Friday. Tacoma, Wash. Contact: Mrs. Maxine Bailey, College of Medical Education, University of Puget Sound, 1500 N Warner, Tacoma, WA 98416. (206) 756-3152.

March 17-18—**Surgery of the Liver and Biliary Tract.** Friday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

March 22-24—**Antibiotics and Infectious Disease—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, March 22, Great Falls. Contact: Mr. John Breeden, PO Box 2829 Great Falls, MT 59403. (406) 453-1493. Thursday, March 23, Billings. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, March 24, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

March 24-25—**Gynecologic Cancer.** Friday-Saturday. Glasier Auditorium, Swedish Hospital and Medical Center. Contact: Dept. of Med. Ed., Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2266.

March 27-28—**Premature Coronary Artery Disease and Lipoprotein—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, March 27, Wenatchee. Contact: William M. McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, March 28, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

March 30-31, April 6-7—**Endocrine Glands.** Thursdays-Fridays. 8 am-10 am, Good Samaritan Hospital, Puyallup, Wash. Contact: Mrs. Maxine Bailey, College of Medical Education, University of Puget Sound, 1500 N Warner, Tacoma, WA 98416. (206) 756-3152.

April 5—**Headaches—Univ. of Wash. General Medicine Sessions in Anacortes, Washington.** Contact: Harry Eiesland, MD, 24th and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

April 5, 12, 19, 26—**Potpourri.** Wednesdays, 8-10 a.m., Tacoma General Hospital, Tacoma, Washington. Contact: Mrs. Maxine Bailey, College of Medical Education, University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

April 9-13—**Pediatric Pulmonary Disease—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Sunday-Monday, April 9-10, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Tuesday-Wednesday, April 11-12, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, April 12-13, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 11-12—**Antibiotics Use in the Surgical Patient—Univ. of Wash. Surgical Program in Montana.** Tuesday, April 11, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59401. (406) 454-1493. Wednesday, April 12, Billings. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Wednesday, April 12, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

April 13-15—**Refresher Course in Diagnostic Radiology.** Thursday-Saturday. Sacred Heart Medical Center, Spokane, Washington. 6 hrs. Fee: $80. Contact: Mrs. Eunice Fisher, Dept. of Radiology, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-3330.

April 21-22—**First Annual Spring Medical-Surgical Conference.** Friday-Saturday, Elks Club, Lewiston, Idaho. 14 hrs. Fee: Before Apr. 1, $75; after Apr. 1, $90. Contact: Kenneth L. Judy, MD, St. Joseph's Hospital, P.O. Box 816, Lewiston, ID 83501. (208) 743-2511.

April 24-25—**Gynecologic Oncology—Univ. of Wash. Obstetrics and Gynecology Program in Idaho and Washington.** Monday, April 24, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391. Tuesday, April 25, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 24-25—**Pulmonary Disease, Part II—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, April 24, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, April 25, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

April 26—**Pacemaker Indications, Selection and Follow-up—Univ. of Wash. General Medicine Program in Anacortes, Washington.** Contact: Harry Eiesland, MD, 24th and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

April 26-28—**Interpretation of Cardiac Data, Valvular Heart Disease—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, April 26, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, April 27, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, April 28, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

May 1-4—**Pediatric Orthopaedics—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Monday, May 1, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Tuesday-Wednesday, May 2-3, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, May 3-4, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 5-6—**ENT Head and Neck.** Friday-Saturday. Glasier Auditorium, Swedish Hospital and Medical Center, Seattle. Contact: Dept. of Med. Ed., Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2266.

May 8-9—**Advances in Contraception—Univ. of Wash. Obstetrics and Gynecology Program in Idaho and Washington.** Monday, May 8, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391. Tuesday, May 9, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 11-12—**Practitioner's Approach to Renal Disease.** Thursday-Friday. Virginia Mason Medical Center, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 19-20—**Medical Applications of Diagnostic Ultrasound.** Friday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 22-23—**Radiologic Aspects of Renal Disease—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, May 22, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, May 23, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

May 24-26—**Clinical Rheumatology—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, May 24, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, May 25, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, May 26, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

Index to The Western Journal of Medicine Advertising

A. MASON BLODGETT & ASSOCIATES INC. 38
AMERICAN ASSOCIATION FOR CLINICAL IMMUNOLOGY AND ALLERGY 31
BOEHRINGER INGELHEIM LTD.
Catapres 14, 15, 16
BURROUGHS WELLCOME CO.
Neosporin Topical 19
Empirin Compound c Codeine 41
CLASSIFIED 34, 36, 38
CMA ANNUAL POSTGRADUATE INSTITUTES 39
DEFENDERS MUTUAL INSURANCE COMPANY 37
THE DOCTORS' COMPANY 23
DORSEY LABORATORIES
Recommendables 12, 13
ELI LILLY AND COMPANY
Kefzol I.M./I.V. 45
ENDO INCORPORATED
Percocet 5 ..... 26, 27
GEIGY PHARMACEUTICALS
Brethine 9, 10
HAWAIIAN CONFERENCE SERVICES
Diving Medicine 26
MARSH & McLENNON 21
MEAD JOHNSON LABORATORIES
Quibron 17
Vasodilan 18
MEDICAL WORLD NEWS 28
MERCK SHARP & DOHME
Aldomet 29, 30
NATIONAL MEDICAL ENTERPRISES INC. 26
PARKE, DAVIS & COMPANY
Povan 8
PHARMACEUTICAL MANUFACTURERS ASSOCIATION 24, 25
PHYSICIANS AND SURGEONS INSURANCE EXCHANGE 32
PHYSICIANS PROGRAMS INC.
Cardiovascular Diseases 5
PVO INTERNATIONAL
Saffola 22
ROCHE LABORATORIES
Gantanol ..... 2nd Cover, 1, 2
Valium ..... 3rd and 4th Covers
SMITH, KLINE & FRENCH CO.
Dyazide 11
SOCIETY FOR CONTINUING MEDICAL EDUCATION
Symposium: Gynecologic Oncology 2
SOMATICS CONFERENCE ASSOCIATES
Explorers of Humankind 20
SYNTEX LABORATORIES INC. 3
UC SANTA CRUZ EXTENSION
Conferences on Stress 2
THE UPJOHN CO.
Tolinase 43
WARREN-TEED PHARMACEUTICALS INC.
Kaon Elixir-Kaon Tabs 6, 7
WORLD HEALTH INFORMATION SERVICES INC.
Symposium: Depression Today 35

THE WESTERN Journal of Medicine

VOLUME 128 • NUMBER 4 **APRIL 1978**

279 *St. Louis Encephalitis in Children*
ALLEN M. KAPLAN, MD; WILLIAM L. LONGHURST, MD, and DONALD L. RANDALL, MD

282 *Cardiopulmonary Resuscitation in Rural Community Hospitals* GEORGE H. HESS, MD

285 *Clinical Diagnosis of Psychogenic Rheumatism* MICHAEL D. REYNOLDS, MD

291 *Femoral Tibial Bypass Grafts—The Alternative to Amputation* GORDON SPROUL, MD

MEDICAL PROGRESS
294 *The Laboratory Diagnosis of Megaloblastic Anemias* RALPH CARMEL, MD

SPECIALTY CONFERENCE
305 *Chronic Hepatitis B*
Participants: JOHN C. HOEFS, MD; ROBERT L. PETERS, MD; ALLAN G. REDEKER, MD; MYRON J. TONG, PhD, MD; JAMES W. MOSLEY, MD, and TELFER B. REYNOLDS, MD
Interdepartmental Conference, Hepatology Division, Department of Medicine, and Department of Pathology, University of Southern California School of Medicine, and John Wesley County Hospital, Los Angeles

MEDICAL STAFF CONFERENCE
318 *California's Natural Death Act*
Moderator: H. HARRISON SADLER, MD
Participants: JULIUS R. KREVANS, MD; BENSON R. ROE, MD; HON. BARRY KEENE; ALBERT R. JONSEN, PhD; JOHN SOLTERS, MD; KATHLEEN R. LAVERY, BSN, RN; ELAINE FRIPP, MPH; HILLARY F. DON, MD, and JEROME LACKNER, MD

329 *Survey Results After One Year's Experience With the Natural Death Act* MURRAY KLUTCH

IMPORTANT ADVANCES IN CLINICAL MEDICINE
331 *Radiology—Epitomes of Progress*

EDITORIALS
337 • *Health Systems Agencies and Local Physicians* • *Diagnosing Megaloblastic Anemias* • *A Study of Potentially Compensable Events* • *Prognostic Determinants in Chronic Hepatitis B Infection—A Reevaluation*

CASE REPORTS
343 *Acute Renal Failure Associated With Hemodialysis and Hypophosphatemia*
STUART LAIKEN, MD, PhD; CLYDE H. BECK, JR, MD, and RICHARD M. TIMMS, MD

345 *Fibromuscular Hyperplasia of External Iliac Arteries* MICHAEL K. DASKALAKIS, MD

347 *Retroperitoneal Emphysema After Colonoscopic Polypectomy*
SIDNEY YASSINGER, MD; ROBERT C. MIDGLEY, MD; DAVID S. CANTOR, MD; TOMMY POIRIER, MD, and THOMAS J. IMPERATO, MD

CORRESPONDENCE
351 • *The Science and the Art* • *Trends in Obstetrics* • *President Lincoln's Illness* • *Registered Nurses and Long-Term Care* • *More on Libraries*

MEDICAL EDUCATION
355 *The Central San Joaquin Valley Area Health Education Center* EDWIN F. ROSINSKI, EdD

SPECIAL ARTICLE
360 *Medical Insurance Feasibility Study—A Technical Summary* DON HARPER MILLS, MD, JD

COMMENTARY
366 *Why Patients Choose Homeopathy* ROBERT L. AVINA, MD, and LAWRENCE J. SCHNEIDERMAN, MD

MEDICAL INFORMATION
370 *Tracheoesophageal Fistula and Associated Malformations*
C. RICHARD DEWAR, MD; STEPHEN R. SHAPIRO, MD, and DAVID F. MERTEN, MD

373 *Book Reviews*

376 *In Memoriam*

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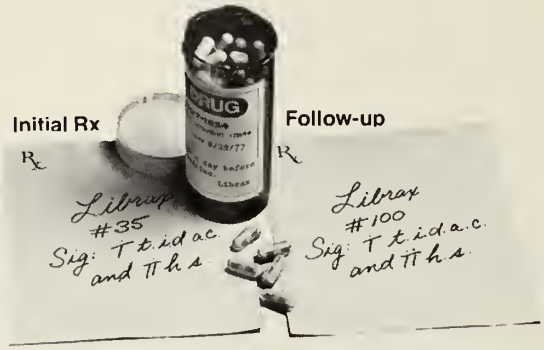

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Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated, avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

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Volumes begin with the first of January and the first of July. Subscriptions may commence at any time.

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Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

FOR LONG-TERM CONTROL OF HYPERTENSION.* SERUM K^+ AND BUN SHOULD BE CHECKED PERIODICALLY. (SEE WARNINGS SECTION.)

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Tablets contain 5 mg. (equivalent to 4.1 mg. of free base) or 2.5 mg. (equivalent to 2.05 mg. of free base) of Brethine, brand of terbutaline sulfate.

Indications: As a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Contraindications: Known hypersensitivity to sympathomimetic amines.

Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child.

Usage in Pediatrics: Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, and hyperthyroidism. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias. Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy.

Adverse Reactions: Commonly observed side effects include nervousness and tremor. Other reported reactions include headache, increased heart rate, palpitations, drowsiness, nausea, vomiting, and sweating. These reactions are generally transient in nature, usually do not require treatment, and appear to diminish in frequency with continued therapy. In general, all the side effects observed are characteristic of those commonly seen with sympathomimetic amines.

How Supplied: Round, scored, white tablets of 5 mg. in bottles of 100 and 1,000 and Unit Dose Packages of 100; oval, scored, white tablets of 2.5 mg. in bottles of 100.

(B) 98-146-060-E (Rev. 4 76)667004 C76-12

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1. Morse, J.L.C., et al: Am Rev Respir Dis *113*:89-91 (Jan.) 1976.
2. Allegra, J., et al: J Clin Pharmacol: 367-370 (July) 1976.

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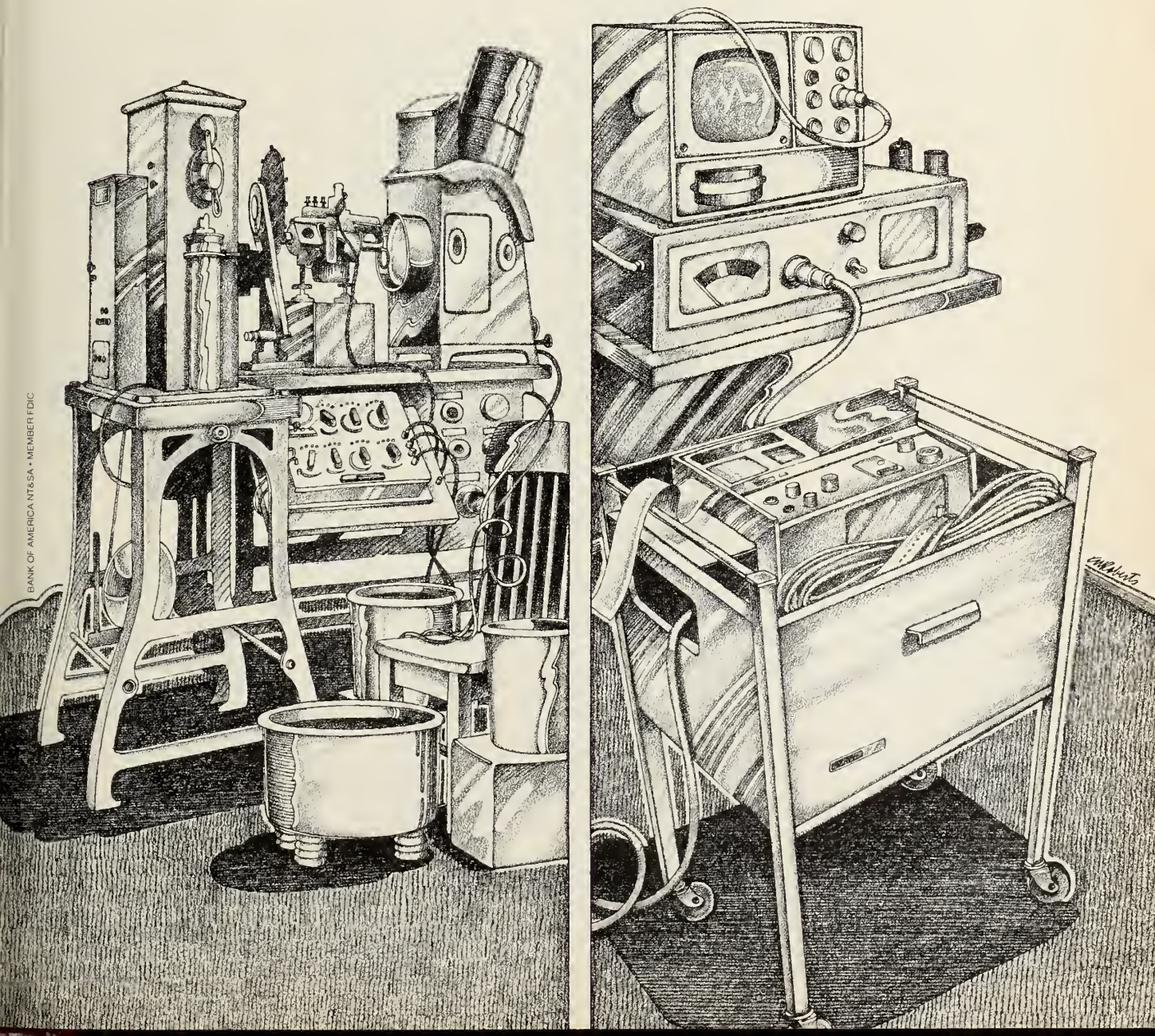

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In TV commercials, you'll often see people speaking up for milk. Steve Allen and his wife Jayne Meadows are also seen on TV telling viewers about Mocha Mix... 100% milk free!

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NUTRITION INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)
Servings Per Container 16
Calories 40
Protein . . . . . 0 grams
Carbohydrate . . . . . 3 grams
Fat . . . . . 3 grams
Percent of Calories from Fat 73%
Polyunsaturated Fat . . 1 gram
Saturated Fat . . . . . 0 grams
Cholesterol (Δ) . . . . . 0 mg (0 mg/100g)

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

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Time is the test of all things.

1954
1978

BRIEF SUMMARY

Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. May be used in the treatment of cardiac arrhythmias due to digitalis intoxication.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.

Precautions: Potassium intoxication by oral administration rarely occurs in patients with normal kidney function, however, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

In hypokalemic states, especially in patients on a low-salt diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation.

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The most severe adverse effect is hyperkalemia.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications". Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Kaon® Elixir
(potassium gluconate)
20 mEq per 15 ml

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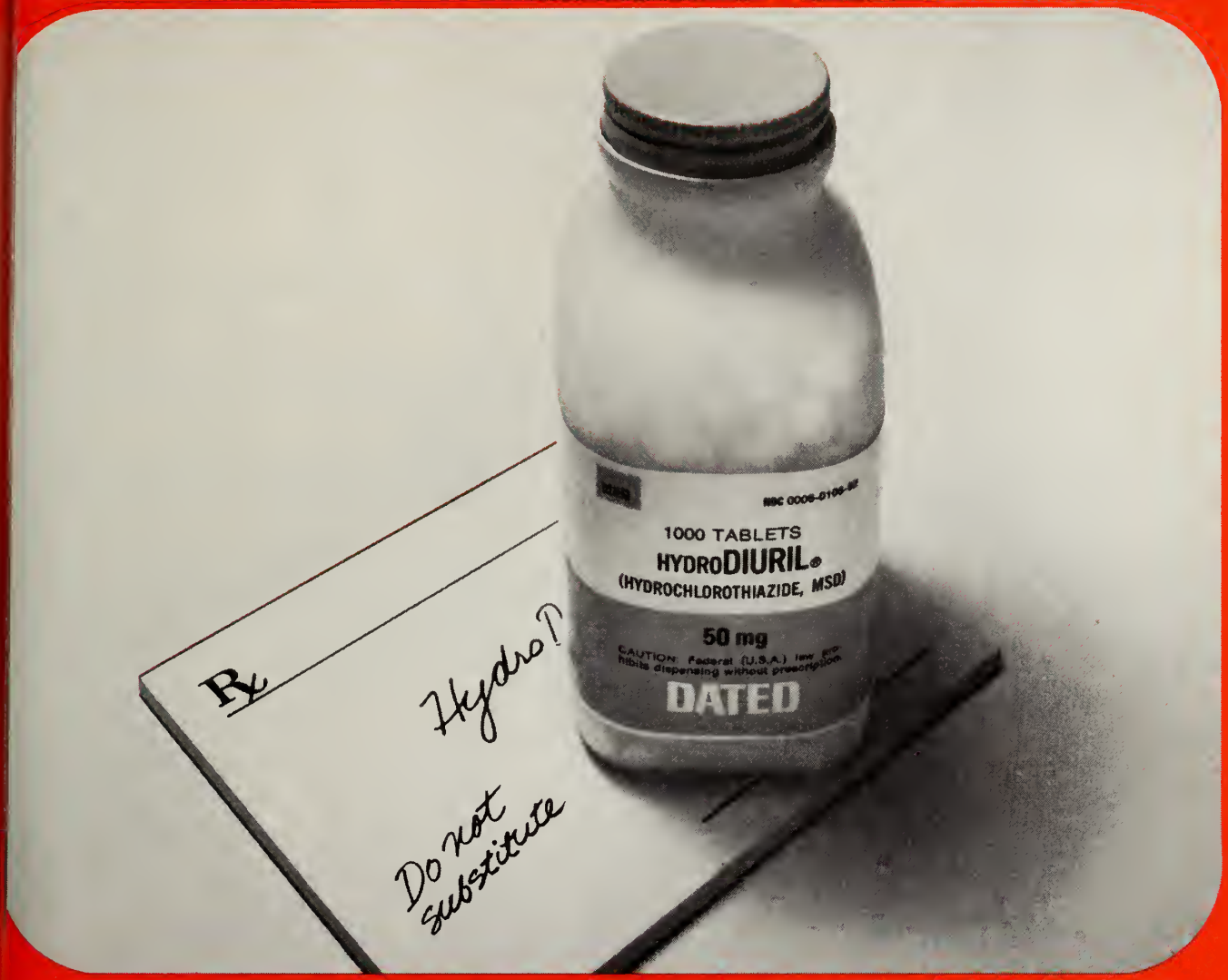
LABORATORIES, INC.
DIVISION OF **ADRIA LABORATORIES INC.**
COLUMBUS, OHIO 43215

There is no substitute

yours...

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs.
Warnings: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy. *Use in Pregnancy*: Thiazides cross placental barrier and appear in cord blood; in pregnancy, weigh anticipated benefit against possible hazards to fetus, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults. *Nursing Mothers*: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.
Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nause and vomiting. Hypokalemia may develop, especially with brisk diuresis in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, c with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increase ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in post-sympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal im-

for experience—



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pairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.
Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.
Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.
Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).
Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.
Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

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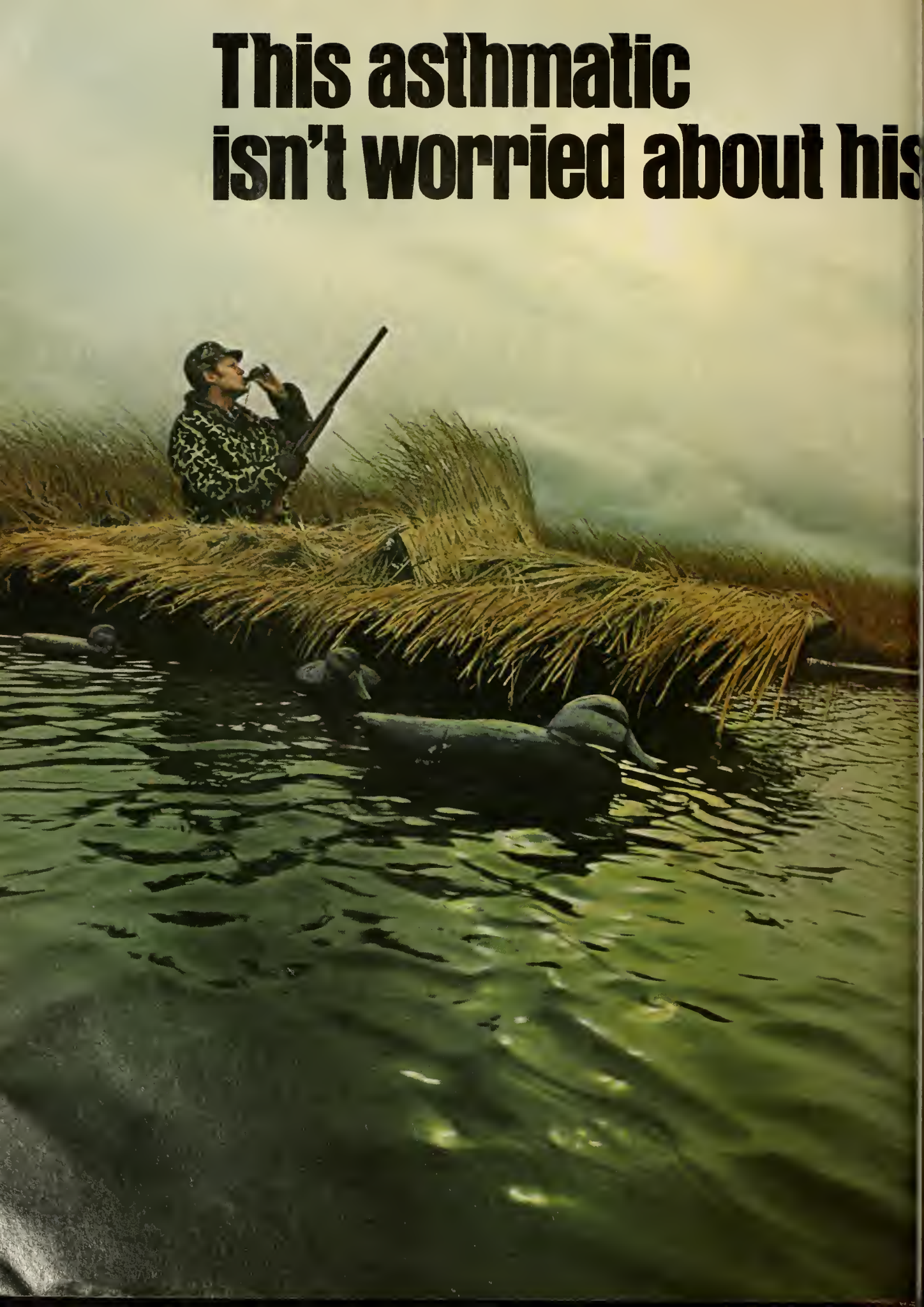

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Precautions: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other xanthine derivatives concurrently. Use in case of pregnancy only when clearly needed.
Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 μg/ml.
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THE WESTERN
Journal of Medicine

Refer to: Kaplan AM, Longhurst WL, Randall DL: St. Louis encephalitis in children. West J Med 128:279-281, Apr 1978

St. Louis Encephalitis in Children

ALLEN M. KAPLAN, MD; WILLIAM L. LONGHURST, MD, *and* DONALD L. RANDALL, MD,
Phoenix, Arizona

St. Louis encephalitis is not an uncommon cause of seasonal meningoencephalitis in children. The clinical presentation is variable and may range from inapparent infection to a severe illness with diverse neurologic signs. A review of three recent cases of St. Louis encephalitis in children in Phoenix, Arizona, stresses the need to consider this type of encephalitis in patients with signs of brain stem dysfunction or acute cerebellar ataxia. The appearance of these clinical signs is supported by the pathologic changes that have been documented to occur, most frequently in the thalamus and brain stem. The importance of serologic identification to facilitate early vector control is emphasized.

St. Louis encephalitis (SLE) is one of several Group B arbor viruses causing seasonal meningoencephalitis in humans. Although children are less frequently affected than adults, several cases of SLE have occurred in the pediatric age group over the past several summers in the Phoenix area. The clinical presentation of SLE in children is quite variable, but usually conforms to the established clinical classification, which includes (1) encephalitis, (2) aseptic meningitis, (3) febrile illness with headache and (4) nonspecific illness types.[1] The majority of infections due to SLE, however, are subclinical or inapparent and have been estimated to occur in a 64 to 1 ratio of subclinical to clinical cases.[2] The purpose of this report is to review the Phoenix cases of SLE in children and emphasize the need to consider SLE in patients with signs of brain stem or acute cerebellar dysfunction.

From the Department of Pediatric Neurology, Good Samaritan Hospital, Phoenix, and the Department of Pediatrics, Phoenix Indian Medical Center, Phoenix.

Submitted October 3, 1977.

Reprint requests to: Allen M. Kaplan, MD, Good Samaritan Hospital, 1033 East McDowell Road, Phoenix, AZ 85006.

Reports of Cases

Case 1. A 4-year-old American Indian child was admitted to the Phoenix Indian Medical Center in the late summer with a five-day history of fever and progressive lethargy. On physical examination at admission the child was febrile and somnolent, with no apparent neurologic localizing signs. A leukocyte count was 20,600 with 81 percent polymorphonuclear leukocytes (PMN), 8 percent bands and 10 percent lymphocytes. A lumbar puncture showed clear cerebrospinal fluid (CSF) with 86 leukocytes per cu mm with 90 percent lymphocytes. The CSF glucose was 59 mg per dl, and the total protein was 42 mg per dl. Viral cultures of the throat, stool and CSF were negative. Acute and convalescent sera for SLE titers

TABLE 1.—*St. Louis Encephalitis Antibody Titers*

Case	*Acute Sera*		*Convalescent Sera*	
1.	<1:8	CF	1:64	CF
2.	<1:8	CF	1:64	CF
	1:10	HI	1:80	HI
3.	1:8	CF	1:32	CF
	1:320	HI		

CF = complement fixation antibody titer
HI = hemagglutination inhibition titer

were drawn (Table 1). The hospital course was characterized by rapid improvement in fever and level of consciousness, and the child was normal on discharge after a seven-day hospital stay.

CASE 2. A 4-year-old Spanish-American girl was admitted to Maricopa County Hospital in the late summer with a five-day history of fever, irritability and anorexia, and a generalized seizure of five minutes' duration immediately before admission. On neurologic examination the child was semicomatose, with obvious right-sided facial weakness and a Parinaud-like syndrome characterized by tonic (downward) vertical gaze with absent vertical oculocephalic reflexes and Bell phenomenon. The tone was generally increased, and decerebrate posturing was intermittently observed. The deep tendon reflexes were increased with clonus in the lower extremities, and bilateral Babinski signs were present. A leukocyte count was 9,600 with 70 percent PMN, 10 percent bands and 20 percent lymphocytes. A lumbar puncture showed hazy CSF. There were 440 leukocytes per cu mm with 84 percent lymphocytes. The CSF glucose was 63 mg per dl, and the total protein was 84 mg per dl. Viral cultures were negative. Acute and convalescent sera for SLE titers were drawn (Table 1). The hospital course was characterized by gradual improvement of most neurologic findings, and the child was discharged after a week in hospital. On follow-up examination a persistent neurologic deficit was noted, with mild truncal and extremity ataxia and dysarthric speech.

CASE 3. A 2-year-old American Indian boy presented to an outlying Indian Health Service clinic in the late summer with a history of fever and a generalized convulsion of two minutes' duration. The child was started on a regimen of phenobarbital (4 mg per kg of body weight per day) and was transferred to Phoenix Indian Medical Center for evaluation. On physical examination at admission, the child was alert but refused to walk. There was noticeable tremulousness and titubation on standing, and there was pronounced ataxia when he attempted to take steps. Cranial nerve and sensory examinations were normal. The deep tendon reflexes were hyperactive on the right side, but there were no Babinski signs. A leukocyte count was 21,000 with 60 percent PMN, 3 percent bands and 37 percent lymphocytes. On lumbar puncture, CSF was clear with 130 leukocytes per cu mm with 96 percent lymphocytes. The CSF glucose was 49 mg per dl, and the total protein was 88 mg per dl. Viral cultures were negative. A phenobarbital level was 9.4 μg per ml. Acute and convalescent sera for SLE titers were drawn (Table 1). The hospital course was one of gradual improvement in balance and gait, and the child was normal on discharge after an eight-day hospital stay.

Discussion

SLE was first recognized during a limited epidemic in Paris, Illinois, in 1932. The following year, however, the virus was identified in epidemic proportions in St. Louis, Missouri, and hence the name St. Louis encephalitis. Since that time, SLE has occurred sporadically and infrequently in epidemics in many states, but appears to be most prevalent in the southwestern United States. More than 540 cases of SLE were confirmed in 1975, and an additional 157 cases were reported in 1976.[2] Although statistics for 1977 are incomplete, 29 cases have been documented for that year.

The disease is transmitted by the Culex mosquito and occurs most frequently in the summer and early fall months. As other viral encephalitides, the clinical signs of SLE are variable and range from inapparent infection with imperceptible neurologic signs to a severe illness leading to death. In general, children with SLE usually present with fever, headache, emesis, and signs of meningeal irritation. Other clinical manisfestations include seizures, altered sensorium, tremor, varying degrees of pyramidal tract dysfunction, and less frequently cerebellar and cranial nerve involvement. The mortality rate in children is usually low (0-22 percent), but neurologic residua may occur in as many as 50 percent of cases.[3] These sequelae are most commonly disturbances of gait and equilibrium, behavioral problems, deafness, disorders of speech and persistence of cortical-spinal tract signs.[3-6] Although there are no characteristic laboratory signs, our patients had

consistent CSF lymphocytosis and a peripheral PMN leukocytosis. The diagnosis of SLE is confirmed by a fourfold or greater rise in the complement fixation and hemagglutination inhibition antibody titers between acute and convalescent sera.

The gross pathologic changes seen in SLE include a nonsuppurative inflammatory reaction of the brain and meninges with diffuse vascular congestion and edema. The microscopic changes are characterized by a monocytic cellular infiltrate with typical perivascular cuffing and glial nodules. Neuronal degeneration may occur, as well. Although all levels of the nervous system may be affected, observers describe the pathologic changes to occur most frequently in the regions of the thalamus and brain stem.[4,7,8]

Treatment of SLE is mainly supportive. There is currently no available SLE vaccine, and control of the disease is directed toward elimination of the mosquito vector. The authors, therefore, emphasize the need to serologically identify possible arboviral infections in patients with seasonal meningoencephalitis to facilitate early vector control.

Although Case 1 in our review conforms to the typical presentation of SLE with meningoencephalitis, our other cases are in some ways unique. Case 2 illustrates predominant brain stem dysfunction characterized by 7th nerve paresis, decerebration and a Parinaud-like ocular syndrome, and case 3 documents acute cerebellar ataxia. Although this latter syndrome has been associated with occult neuroblastoma,[9] infectious mononucleosis[10] and numerous other viral infections, it has not previously been reported with SLE. In view of these above facts, the importance of considering SLE in any patient presenting with signs of meningoencephalitis, brain stem encephalitis and acute cerebellar ataxia is to be stressed.

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Refer to: Hess GH: Cardiopulmonary resuscitation in rural community hospitals. West J Med 128:282-284, Apr 1978

Cardiopulmonary Resuscitation in Rural Community Hospitals

GEORGE H. HESS, MD, *Carson City, Nevada*

Carson-Tahoe Hospital is a 77-bed hospital serving a large rural area. During 22 months cardiopulmonary resuscitation was carried out 89 times in 79 persons. Of these resuscitations, 56 were done in the emergency room and 25 on inpatients. Resuscitation was successful in 46 percent of the patients at least once, and 30 percent of the patients lived and were released. These figures compare favorably with those from larger, urban centers, despite problems unique to smaller hospitals.

REDUCING NUMBERS OF DEATHS by extending life-saving and life support methods beyond hospital walls has become a major goal in many centers.[1] In urban areas reduced morbidity and mortality have been reported with such efforts.[2,3] Rural areas with their greater distances, transportation problems and sparse populations would appear to be less than ideal for successful application of these methods.[4] In addition, it would seem difficult for small hospitals without house staffs to match statistics from larger centers.

Carson-Tahoe Hospital is a 77-bed hospital, located in Carson City, Nevada. In addition to serving Carson City, it serves all or part of five Nevada counties and portions of two California counties in an area 50 miles wide by 60 miles long (see Figure 1). An estimated 40,000 people lived within this area at the time of the study and it is constantly visited by a large, but variable, number of tourists. Transportation over mountain highways and passes presents major challenges to providing prehospital medical care.

Cardiopulmonary resuscitations (CPR) at Carson-Tahoe Hospital were reviewed by the Medical Pediatrics Committee and the results of that review are the subject of this report. Inpatient as well as emergency room CPR's are included.

From the Departments of Medicine and Pediatrics, Carson-Tahoe Hospital, Carson City, Nevada.

Submitted November 30, 1977.

Reprint requests to: George H. Hess, MD, Carson Medical Group, Carson Medical Center, Carson City, NV 89701.

Methods

All CPR's carried out between January 1975 and October 1976 were reviewed. CPR was done 89 times in 79 persons. However, eight persons in whom CPR was carried out were judged dead on arrival because of the findings of fixed, dilated pupils; absence of any spontaneous respiratory and cardiac activity; lack of electrical cardiac activity, and absence of response to any of the resuscitative efforts.

In the remaining 71 persons, CPR was carried out 81 times. Of this number, 56 of the procedures were done in the emergency room on newly arrived patients and 25 on inpatients. Careful review of these records showed that the care generally conformed to the standards for cardiopulmonary resuscitation published by the National Conference on Cardiopulmonary Resuscitation in 1974.[5]

Results

Table 1 separates the inpatient and emergency room CPR's and lists the number of successful and unsuccessful resuscitations. An overall success rate of 45 percent was achieved. Table 2 lists the results in the total number of patients; 33 of 71 (46 percent) were successfully resuscitated at least once. Of these patients, 21 left the hospital alive. Therefore, 30 percent of the patients in whom CPR was done, nearly two thirds of those successfully resuscitated, left the hospital alive.

Table 3 compares these results with those found in the literature.[2,6-8]

Table 4 separates the emergency room CPR patients by geographic origin and includes those judged dead on arrival. A 36 percent survival rate was obtained in both urban Carson City (18 of 50) and the rural area (5 of 14). When the dead-on-arrival patients were excluded, the figures are 39 percent for Carson City (18 of 46) and 50 percent for the rural area (5 of 10).

The duration of all in-hospital CPR's was also reviewed. They ranged from 6 minutes to 90 minutes, with an average time of 28 minutes. For emergency room CPR's it was impossible to determine the time of initiation of CPR and, therefore, duration could not be calculated.

Discussion

The results of the study compare favorably with those reported from other centers despite the unique problems of a small community hospital. These problems include the following:

- No house staff.
- A large service area.

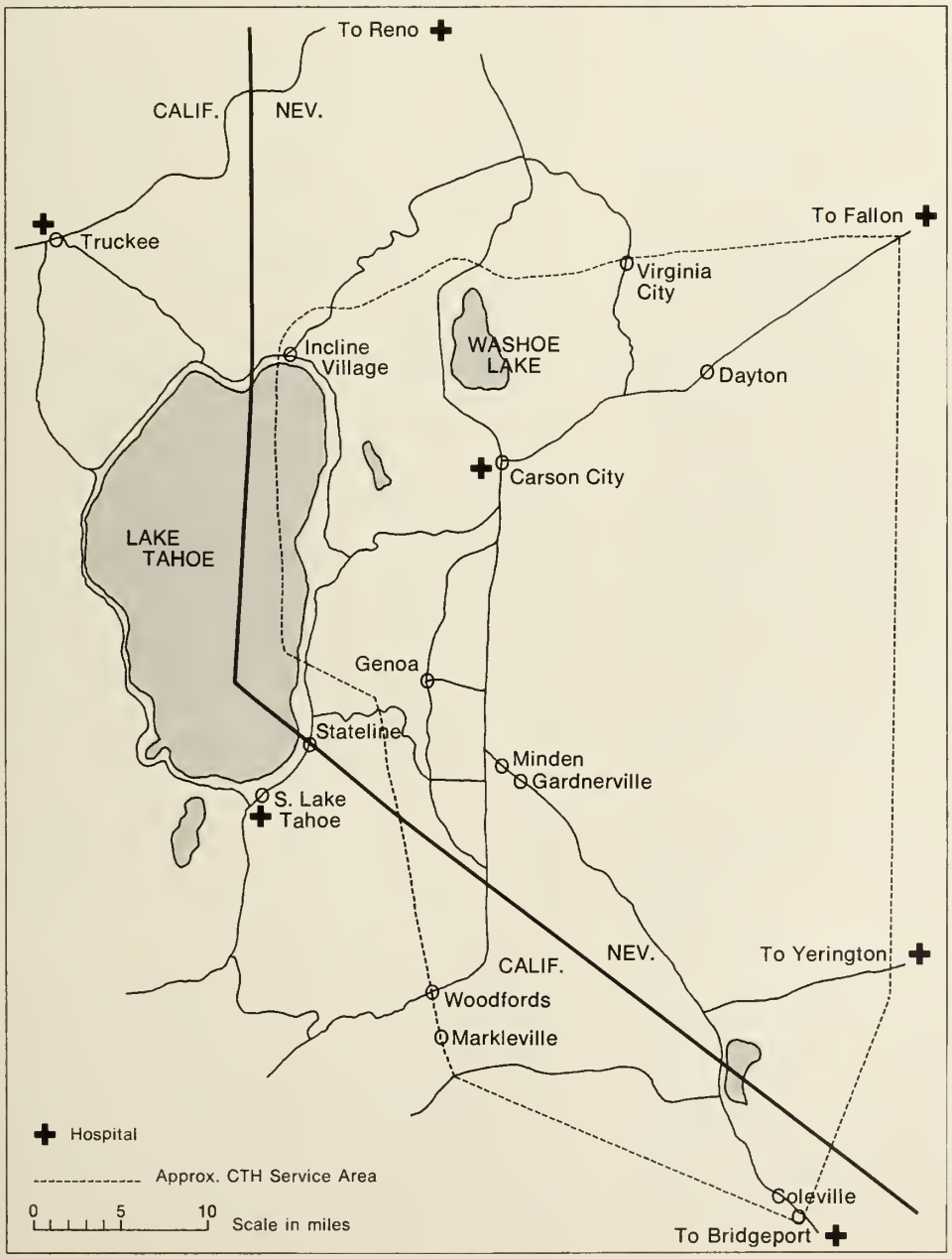

Figure 1.—Carson-Tahoe Hospital service area.

TABLE 1.—*Number of Successful and Unsuccessful Resuscitations in 81 Attempted Resuscitations*

Site	Attempted Resuscitations	Deaths	Survivors Number	Survivors Percent
Emergency room	56	33	23	41
Inpatient	25	11	14	54
Totals	81	44	37	45

TABLE 2.—*Number of Patients Successfully Resuscitated and Number Discharged*

	Patients	Percent
Total	71	100.0
No. resuscitated	33	46.4
No. discharged	21	29.6

- Limited financial resources.
- Involvement of multiple fire departments, police agencies and counties, and—in our case—two states.
- Changeable weather and mountain highways.

A number of factors appear to have contributed to the success at Carson-Tahoe Hospital:

- An enthusiastic nursing staff, with excellent basic training and periodic refresher courses.
- Full-time emergency room staff, which responds to all cardiopulmonary resuscitations.
- Three on-call physicians responding to all CPR's. These include the on-call family physician, surgeon or internist and anesthesiologist. The first of these physicians on the scene is in charge of the resuscitative efforts until the patient's personal physician arrives.
- In addition, a respiratory therapist and an intensive care unit nurse always respond.
- An excellent emergency medical technician (EMT) program in which nearly 400 persons have been trained since 1972.

The EMT program deserves special mention because it appears that success in the emergency room is directly attributable to the persons trained in this program. The program is supervised by emergency room physicians and includes 80 hours of rigorous training. An attempt has been made to train those persons most likely to arrive on the scene first. Consequently, most firemen, police and highway patrol officers, sheriff's deputies, state park and forestry rangers, and ambulance attendants have completed the course. In addition, all members of Sierra Search and Rescue, many casino employees and many ski patrolmen also have been trained.

TABLE 3.—*Comparison of Cardiopulmonary Resuscitation Results*

	Number Patients	Percent Successful	Percent Discharged Alive
Carson-Tahoe	71	46.4	29.6
Denver[7]	201	36	17.5
Montreal[6]	1204	..	19
Seattle[2]	..	..	18-40
Hurst and Logue[8]	..	15-40	2-20

TABLE 4.—*Origin of Emergency Room Patients and the Results of Cardiopulmonary Resuscitation*

Origin	Dead on Arrival	Deaths	Total Deaths	Survivors	Total Patients
Carson City	4	28	32	18	50
Minden-Gardnerville	2	2	4	4	8
Genoa	0	0	0	1	1
Wellington	0	1	1	0	1
Markleville	0	2	2	0	2
Yearington	1	0	1	0	1
Dayton	1	0	1	0	1
Totals	8	33	41	23	64

Conclusions

Small community hospitals can achieve cardiopulmonary resuscitation results comparable to those reported from larger, urban area centers. Within the hospital, success appears to result from the high level of nursing skill and the cooperative efforts of staff physicians.

Outside the hospital, the presence of a large number of persons, throughout the service area, who are skilled in cardiopulmonary support and first aid seems to be the key to success. It must be acknowledged that some victims died at the scene. These statistics are not readily available for retrospective study because of the many county and state agencies involved. However, it does appear that when trained persons reach the scene before death and initiate effective cardiopulmonary resuscitation, the location and distance from the hospital make little difference in most cases.

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Refer to: Reynolds MD: Clinical diagnosis of psychogenic rheumatism. West J Med 128:285-290, Apr 1978

Clinical Diagnosis of Psychogenic Rheumatism

MICHAEL D. REYNOLDS, MD, *Orange, California*

Rheumatic symptoms that are a somatic expression of emotional disturbance are common, and often are mistakenly attributed by physicians to organic disease. Psychogenic rheumatism is encountered most frequently among middle-aged women. The typical complaint is of widespread pain and stiffness, often with report of swelling and paresthesia, but symptoms characteristically are vague. Overt psychiatric disturbance may be apparent. Distinction from organic disease should not be difficult if physicians recognize the typical presentation, and find that symptoms fail to correspond to patterns of organic disorders. When organic disease coexists with psychogenic rheumatism, as often is the case, the objective abnormalities are insufficient to explain the symptoms.

Persons who suffer from psychoneurotic illness not infrequently develop a symptom-complex which includes pains or aches and stiffness or limitation of movement with or without loss of power. This fact has received little emphasis in medical textbooks and has not been systematically disseminated in the teaching of undergraduates.

—JAMES L. HALLIDAY[1]

It is now 40 years since Dr. James Halliday called the attention of his colleagues to the frequency with which rheumatic symptoms occur during emotional disorders,[2] warned how often errors in diagnosis and treatment result from neglect of this fact[3] and introduced the name "psychoneurotic rheumatism." Halliday and later writers found that from 13 percent to 49 percent of patients with rheumatic complaints cannot be shown to have organic disease which explains their symptoms.[2,4-9] Despite its frequency, many physicians experience difficulty in recognizing psychogenic rheumatism (PR), or in diagnosing it with confidence. Discussions in textbooks,[10] as well as published series of cases,[2,6,7,11-13] describe many valuable diagnostic features, but do not consider whether characteristics frequently noted in patients with PR are also seen in persons with organic rheumatic disease. Furthermore, these descriptions tend to deal with "pure cases," in which no concurrent organic disorder confuses the clinical presentation. However, structural musculoskeletal disease frequently coexists with PR.[4,7,9] For these reasons, an analysis of the clinical features of PR compared with those of common organic articular diseases should be useful.

Materials

The records of all consultations by the author during a four year period were reviewed; of these 135 were abstracted with special attention to features that clinical observation and the literature had suggested were frequent in PR. These 135 cases consisted of all in which the principal diagnosis was PR or one of the three most prevalent diseases of joints: rheumatoid arthritis ("definite" or "classical" by criteria of The American Rheumatism Association[14]), degenerative joint disease

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Supported by a grant from The Arthritis Foundation, Southern California Chapter.

Submitted August 15, 1977.

Presented in part at the VIII European Rheumatology Congress, Helsinki, Finland, June 5, 1975.

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(osteoarthritis) or degenerative intervertebral disk disease. In addition, all cases of predominantly musculoskeletal symptoms, in which no specific diagnosis was made, were analyzed. This was done to examine whether PR was being diagnosed because of specific features or merely by exclusion.[7,12,13,15]

Results

The characteristics of the five groups of patients are shown in Table 1. Symptoms elicited from the patients are given in Table 2.* It is apparent that the classes of symptoms reported by patients with PR are similar in type and frequency to those of persons with organic articular disease. However, the frequency of paresthesias[7,16] differs between PR and the other conditions, except disk disease, to a statistically significant degree ($p<0.05$ by chi-square method).

Clues to the presence of PR can be found both in interviews and in physical examinations of patients. Evidence of the disease in the patients' histories is found in the *character of the symptoms,* the *patient's manner of describing the illness* and the history of *previous medical care* (Table 3).

Features of Symptoms Reported by Patients

Three features of the rheumatic symptoms reported commonly by patients with PR were unusual in other groups:

Imprecise Symptoms.[7,17] There are two aspects to the feature of imprecise symptoms. First, patients with PR are unable to indicate pain in specific structures; they locate symptoms only by indicating regions. Typically pain is noted both

*Patients are tabulated under the disease primarily responsible for their symptoms. However, at least 38 percent had another rheumatic disease, most often degenerative in character. The manifestations shown in the tables may be those of the primary or the second illness. For example, swelling of joints in patients with degenerative disk disease was due to concurrent (degenerative) disease of synovial joints.

TABLE 1.—*Characteristics of Patients Studied*

Diagnosis	*Number*	*Percent Female*	*Mean Age (Years)*	*Age Range (Years)*	*Mean Duration of Illness (Years)*
Psychogenic rheumatism	29	79	43	12-66	6
Rheumatoid arthritis	35	80	54	19-80	10
Degenerative joint disease	27	85	62	17-83	7
Degenerative disk disease	13	71	63	45-78	15
None established	31	68	43	15-76	4

TABLE 2.—*Frequency of Symptoms*

	Percent Frequency of Occurrence with				
Symptoms	*Psychogenic Rheumatism*	*Rheumatoid Arthritis*	*Degenerative Joint Disease*	*Degenerative Disk Disease*	*Undiagnosed*
Musculoskeletal pain	100	100	96	100	100
Swelling of joints	45	86	81	21	65
Stiffness	55	80	30	42	13
Generalized morning stiffness	17	63	4	29	6
Erythema at joints	7	20	15	14	16
Crepitus	10	3	22	47	0
Fatigue	21	43	4	7	16
Paresthesias	31	3	7	36	10

TABLE 3.—*Characteristics of Interviews With Patients*

	Percent Frequency of Occurrence with				
Characteristic	*Psychogenic Rheumatism*	*Rheumatoid Arthritis*	*Degenerative Joint Disease*	*Degenerative Disk Disease*	*Undiagnosed*
Imprecise nature of pain	48	0	4	0	6
Generalized pain	48	3	0	0	3
No relief from treatment	48	0	11	29	13
More than three separate rheumatic complaints	45	3	4	15	3
Prominent non-rheumatic complaints	31	3	0	0	3
Medical words and self-diagnosis	24	3	4	0	3
Prior rheumatic illness or injury	62	26	44	38	16
More than three physicians	31	3	7	31*	3
Psychiatric treatment	41	9	11	31*	3

*Difference between this figure and frequency with psychogenic rheumatism is not significant ($p>0.05$).

in the joints and in interarticular areas. Second, these patients are unable to describe the character of pain in terms such as "sharp" or "aching," or by comparison with familiar pains. Sometimes they use uncommon or dramatic terms to describe symptoms.[11,13,17]

Inability of patients to be precise must be distinguished from the effects of impaired memory,[17] and from the difficulty in obtaining definite answers from patients who are circumstantial or perseverating.

Generalized Pain.[6,7,11,13,17] The feature of generalized pain is well-recognized by most physicians; the patient who "hurts all over" often is mentioned as a prototype of the neurotic patient. When the sites of symptoms are grouped as neck and back (spine), upper limbs and lower limbs, the frequencies with which patients with PR reported involvement of these areas were 83 percent, 93 percent and 100 percent, respectively. The high prevalence of complaints referable to the spine[4] differed significantly from the other groups except, of course, degenerative disk disease. Involvement of all three areas is typical of PR (79 percent of cases).

Frequently the generalized pain is of a transient and migratory character, changing in intensity and location much more rapidly and irregularly than do the symptoms of persons with arthritis. Some patients' descriptions give the impression of a pattern of symptoms changing almost continuously.

Generalized pain should be distinguished from widespread pain. Persons with arthritis or extensive degenerative disease of joints may note pain in many places, but the sites of pain remain discrete, and the patient can easily name places which remain pain-free.

Failure of prescribed treatment to reduce symptoms.[7,13,17] Whereas most of the patients in the other groups reported that treatment had given at least partial relief from pain and other symptoms, nearly half of those with PR indicated that they had gotten no benefit from any treatment prescribed.

Patients' Manner of Describing the Illness

Considering the manner in which patients presented their histories, we noted three features to be characteristic of PR:

Presence of several separable rheumatic syndromes. Patients with polyarthritis usually perceive their illness as a single entity whose sites and intensity vary with time. Persons with degenerative disease of joints may have a few distinct regional syndromes (for example, cervical disk, lumbar disk, knees). But the complaints of those with PR often can be grouped into four, five or more regional sets more or less clearly distinguishable on the basis of their symptoms, temporal patterns, inciting and relieving factors, and the like. This is not just a manifestation of lack of precision in describing symptoms; the patients themselves often perceive their problem as manifold and describe different symptoms in different regions of the body.

Prominent nonrheumatic complaints without evident organic basis.[7] Most of the patients who did not have PR confined their complaints to the musculoskeletal system, during a rheumatological consultation. But nearly a third of those with PR complained, along with rheumatic symptoms, of problems in other organ systems, whose organic basis was inapparent. The colon was the organ most often featured in these nonrheumatic problems, and in several patients extensive studies of the gastrointestinal tract had been carried out.

Use of medical words; self-diagnosis. Patients sometimes offer only a diagnosis when asked to describe their problem. The physician must then ask detailed questions to find out what symptoms lie behind that diagnosis.[15] (Patients with genuine arthritis often will give the diagnosis as a chief complaint, but have no hesitation about describing the symptoms.) In cases of self-diagnosis, a history of reading newspaper and magazine articles or books about the supposed illness may emerge. In other cases, a too-hasty attribution of symptoms to "arthritis," "bursitis" and the like by a physician previously visited has been seized upon by the patient.[15]

Previous Illness and Medical Care of Patients

The final aspect of the interview which indicated the presence of PR was the history of previous illness and medical care.

Previous rheumatic illness or injury. Halliday[2] and others[4,5] have noted the importance of previous rheumatic illness or injury in determining the form or the site of a somatic expression of emotional stress. Previous rheumatic illness was fairly frequent in the other groups, but significantly less so than among the patients with PR.

Consultation with multiple physicians. Another feature is consultation with several physicians regarding the present rheumatic illness.[15] We defined

TABLE 4.—*Physical Findings on Rheumatologic Examination*

Sign	Percent Frequency Found with				
	Psychogenic Rheumatism	*Rheumatoid Arthritis*	*Degenerative Joint Disease*	*Degenerative Disk Disease*	*Undiagnosed*
Tenderness of musculoskeletal structures	90	51	52	85*	65
Generalized tenderness	24	3	0	0	0
Inconsistent manifestations	24	3	0	8	0
Hyperreactivity	7	0	0	0	0
Deformity†	0	71	56	54	3*
Soft tissue swelling or effusion at joints	0	91	41	8*	29
Bony enlargement of joints	21	26*	78	62	13
Crepitus	14	66	74	62	13*
Pain on motion	34	57	48	38*	48
Limitation of motion	24	86	56	85	35
Absence of objective signs of rheumatic disease	48	0	0	0	48*

*Difference between this figure and frequency with psychogenic rheumatism is not significant ($p>0.05$).
†Excluding deformities of the feet, mild degrees of which are frequent in healthy persons.

this as the patient's having, on his or her own initiative, consulted three or more physicians without apparent reason except dissatisfaction. This correlates with the report of failure of treatment to relieve symptoms (above). Patients with disk disease had multiple physician contacts as frequently as did those with PR.

Prior psychiatric treatment. Prior psychiatric treatment was usually in the form of tranquilizers or antidepressants provided by the patients' regular physicians, rather than therapy by a psychiatrist. Patients with disk disease also had frequently received such drugs. A high prevalence of past psychoneurotic illness has been reported in some studies of PR.[4,6,7,16]

Nondiagnostic Features of Histories

In this study, some features which have been said to be typical of PR were not found more often with that disease than with organic disorders.

Female sex of patient. The proportion of women to men was the same as for the other rheumatic disorders (Table 1). Recognized sex-related factors, such as willingness to seek medical attention, preclude any valid statement about a predilection of PR for one sex, in the absence of epidemiologic studies of populations. Many cases of PR in men were collected by military physicians during wartime.[4-6,11]

Absence of visible change in symptomatic areas.[6] Only 31 percent of the patients with PR did not claim some change in the appearance of affected parts. Nearly half reported that they had swollen joints; this symptom usually was not confirmed by examination.[4]

Lack of external inciting or relieving influences on symptoms.[7] Patients with PR commonly stated that their pain was influenced by use of the affected part, and often attributed worsening to inclement weather.

Absence of disability.[13] Report of difficulty in carrying out usual activities was as common among patients with PR as among those with organic disease.

Multiple surgical operations.[15,17] A history of more than three operations was not more frequent in the group with PR.

Family history of rheumatic disease.[4,16] This was very common in all groups. (However, we have seen cases of PR in children in which the symptoms were plainly a pattern of behavior learned from a neurotic mother.)

Marital discord.[16] Separation, divorce or expressed unhappiness with the spouse were not significantly more common in the group with PR. (Despite its small diagnostic value, evidence of marital discord should be sought because it is the major environmental factor in the genesis of some cases of PR.)

Findings on Physical Examination

The findings on physical examination also provide clues to the presence of PR (Table 4). The most frequent finding was tenderness of musculoskeletal structures. A psychogenic basis for reports of tenderness was indicated by a *nonanatomical distribution.*[7,13] The sites reported as tender did not correspond to typical sites of individual rheumatic diseases, to specific anatomical structures, to specific tissues or to patterns of pain reference. One form of this is generalized tenderness (the physical analogue of the symptom of "hurting all over"). A second sign of the nonorganic nature of complaints of pain and tenderness was *incon-*

TABLE 5.—*Psychiatric Syndromes Manifested by Patients*

	Percent Frequency Found with				
Psychiatric Syndrome	*Psychogenic Rheumatism*	*Rheumatoid Arthritis*	*Degenerative Joint Disease*	*Degenerative Disk Disease*	*Undiagnosed*
Depression	17*	0	0	0	6
Anxiety	17	0	0	8	3
Hysteria	7	0	0	0	0
Total	41	0	0	8	9

*In two (7 percent) of the depressed patients there also were manifestations of anxiety.

sistent manifestations.[13,15] Failure of repeat palpation of previously tender sites to provoke renewed signs of discomfort was associated with PR. A more subtle inconsistency was normal posture, movement and gait during the interview, or when the patient was unaware of being observed, which changed to painful, abnormal motor activity during the formal physical examination. Hyperreactivity and withdrawal from the examiner[10] (what Boland[7] has appropriately called a "touch-me-not" response) has been said to be characteristic of PR, but was observed only infrequently in this series. More often, patients with PR reported pain while evincing none of the signs—facial expression, tensing of muscles or withdrawal—which normally accompany a truly painful examination. Such patients might assert "That's *very* sore" in a completely bland manner.

A most important finding was that more than a third of the patients with PR had identifiable joint disease. Degenerative disk disease was present in six and osteoarthritis in four (in one combined with disk disease); one had a "frozen" shoulder and one had congenital disease of a hip. (We have also seen PR occurring with rheumatoid arthritis.) A similar frequency of coexisting organic disease (28 percent to 40 percent) has been noted in previous studies.[4,7,9,11] Important evidence of PR in these cases was that the symptoms did not correspond in their site, character or severity to those expected from the observed lesions; in other words, the *observed organic changes do not explain the symptoms of which the patient complains.*[4] Only about half the patients with PR were completely free of objective signs of rheumatic disease. Nevertheless, the prevalence of most objective signs of articular disease (deformity, soft tissue swelling or effusion, crepitus, limitation of motion) was significantly lower among patients with PR than in the other groups. The exception was the bony enlargement of osteoarthritis, which was present with about equal frequency among those with PR, rheumatoid arthritis and an undiagnosed disorder. The subjective report of pain during motion was significantly less frequent among those with PR than in the other groups.

Diagnosis of a specific psychiatric disorder could be made from the patient's behavior in certain cases (Table 5). Depression was considered to be present when there were a history and an appearance of sadness (including weeping) and of psychomotor retardation, sometimes with supporting symptoms such as morning insomnia. Often an explanatory life situation was uncovered. Anxiety was diagnosed on the basis of an appearance of tenseness and restlessness, and expressions of apprehension and concern. This was sometimes combined with a tendency to fidget continuously with some object in the hands. Two patients reported a plethora of symptoms, but exhibited relative indifference to symptoms, and denial of emotional stress. Their behavior toward the examiner had seductive or sexual overtones. They were thought to qualify for a diagnosis of hysteria. Detailed, formal psychiatric investigation was not attempted; presumably it would have led to a larger number of specific diagnoses.[6,11,16] Specific syndromes were noted significantly more often among patients with PR than among those with organic disease.

Report of a Case

A 55-year-old woman, a nurse's aide retired because of disability, stated "my spine is going to pieces." Seven years previously she had begun to have pain in the neck and head, with weakness and paresthesias in the upper limbs, which progressed over several years to a "pulsating, throbbing" pain in the "whole spine." Roentgenograms showed minimal degenerative cervical and lumbar disk disease, but an electromyogram was abnormal, and anterior fusion of the 5th and 6th cervical vertebrae was done. This relieved symptoms only for a few weeks; a second fusion operation one level higher was equally unsuccessful. The

patient now complained of pain in almost all regions of the body, paresthesias in the limbs and a multitude of other symptoms. Several relatives and the patient's husband were reported to have disease of the spine.

The patient did not readily answer questions about her life situation; she denied any family problems and appeared to have no interests outside her home. During examination she reported tenderness or pain on motion at many sites, but the only objective abnormality was modest limitation of active motion of the cervical spine. Straight leg raising with the patient supine caused pain, but the same maneuver "disguised" while the patient was sitting was painless. Throughout her visit, the patient frequently used medical terms (often incorrectly), and her narrative was burdened with innumerable self-diagnoses and interpretations. There seemed to be considerable latent hostility toward physicians; the patient ascribed some of her symptoms to previous diagnostic procedures and repeatedly mentioned the failure of past treatment to afford her relief. She denied any emotional component to her illness even before any such suggestion was made, and became defensive and uttered a blanket denial when this possibility was mentioned. It may be significant that the rheumatic symptoms began shortly after the patient underwent hysterectomy and oophorectomy; her manner of dress and use of cosmetics were appropriate for a younger woman, perhaps suggesting a sense of loss.

Differential Diagnosis

The patients with PR plainly had created problems in diagnosis for their physicians. In only two cases did a referring physician indicate that he or she recognized the symptoms as possibly psychogenic. However, the frequency with which the patients had received tranquilizers and antidepressants suggests that the emotional aspects of their illness did not fully escape the attention of their physicans.

Astonishingly 11 (38 percent) of the patients with PR reportedly had received a diagnosis of rheumatoid arthritis from a physician, despite the fact that none of them met well-publicized diagnostic criteria for that disease[14] and none had objective findings of inflammation of the joints. Another six patients had been said to have unspecified "arthritis." A number of the patients had been given dangerous drugs such as corticosteroids and phenylbutazone. Confusion of PR with rheumatoid arthritis indicates unfamiliarity with the features of both diseases.

Some physicians have equated PR with the debated clinical entity "fibrositis."[11] So labeling patients whose rheumatic symptoms stem from emotional disturbance may comfort physicians or patients by creating an aura of organicity about the psychogenic disorder. But such mislabeling is likely to impair understanding of the actual causes of the symptoms, and to promote continued ineffective treatment with antirheumatic measures.

The failure of a neurotic patient's symptoms to correspond to an organic entity, and the manner in which he or she presents those symptoms, should often make evident the diagnosis of PR. The physician's role in the course of the illness can be crucial. By making an erroneous diagnosis of "arthritis," by delaying too long in telling the patient any diagnosis or by subjecting the patient to extensive, unrevealing laboratory testing, the physician can increase in the patient's mind the presumption of organic illness, and fix the neurosis more strongly.[4,12,15] This may have occurred in some of the cases in the present study.

Conversely, persons with an organic musculoskeletal disorder and a concurrent neurosis should not be labeled as having PR in the absence of its characteristic manifestations. Nor should the organic rheumatic disease which often accompanies PR be neglected, although evaluation or treatment of the organic condition may be difficult because of the coexisting psychogenic disorder.

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Refer to: Sproul G: Femoral tibial bypass grafts—The alternative to amputation. West J Med 128:291-293, Apr 1978

Femoral Tibial Bypass Grafts

The Alternative to Amputation

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Severe ischemia and distal gangrene of lower extremities due to obstruction of the popliteal artery and its branches need not require major amputation. Autogenous vein grafts to the distal anterior tibial, posterior tibial, peroneal and dorsalis pedis arteries can avoid tissue loss in many instances.

ONE HUNDRED femoral tibial grafts were carried out for threatened limb loss due to gangrene, rest pain and severe ischemia. A total of 85 grafts were initially successful. Lack of collateral connections to the arterial arcades of the foot appeared to influence patency adversely. No other criteria, such as vessel calcification, diabetes or local extent of disease, seemed critical. During the first year, an additional 11 grafts failed. Late failures occurred in four other grafts at 14, 19, 35, and 54 months, respectively. The 68 remaining grafts maintained patency until the patient's death or during follow-up of up to seven years. Major amputations were required in only 19 instances. Limb salvage achieved by this method of treatment suggests its use in limbs presently relegated to primary amputation.

Methods

In 100 severely ischemic or gangrenous limbs, revascularization was carried out using reversed saphenous, cephalic or antecubital veins. All grafts originated at the common femoral or the upper portion of the superficial femoral artery, and terminated in the lower third of the leg or foot. Most of the grafts were to the anterior tibial or dorsalis pedis arteries, but the peroneal and posterior tibial arteries were also used (Table 1). The vessel selected to receive the graft was that which had the most direct communications to the pedal arches (Figure 1). Calcification of the vessels did not preclude a successful procedure. Diabetes, which was present in 60 percent of the patients, did not appear to affect the outcome. Many of these patients were quite elderly; a majority being over 70 years of age (Table 2).

Several technical aspects of the procedure seem important to assure success:

- The use of fine monofilament continuous suture avoids damage to both the vein graft and the small diseased artery.
- Passage of the grafts subcutaneously avoids the trauma inherent in such techniques as removal of a portion of the fibula, or passage through the interosseous membrane. Subcutaneous position assures the avoidance of kinking, and allows easy palpation to determine patency.
- Inflation of the graft with heparinized saline after proximal anastomosis allows passage to the foot or lower leg without rotation.
- Arteriograms after reconstruction may show undetected technical problems and allow immediate correction.

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Submitted, revised, October 25, 1977.

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• No postoperative anticoagulants need be used and ambulation is begun immediately.

Results

Despite the advanced age and diabetic and arteriosclerotic state of these patients, the operations resulted in only three postoperative deaths. The late mortality was appreciable, with 32 patients succumbing to the complications of arteriosclerotic cardiovascular disease and carcinoma; but 15 had open grafts and salvaged limbs. In all, 85 limbs were successfully grafted; two patients died of myocardial infarction in the postoperative period with patent grafts. There were 11 additional graft failures in the first year, and 4 late failures. In all the 15 operative failures, amputation was necessary and in 4 of the later failures, amputation likewise was required—a total of 19 limbs lost. Sixty-eight grafts remained patent until the patient's death or during a follow-up of up to seven years (Table 3). Long-term patency is limited by poor patient survival from advancing age and severe cardiovascular disease. Very few of these elderly patients, who present with severe ischemia or gangrene as a manifestation of their arteriosclerosis, will survive five years. With femoral tibial bypass grafting, it would appear that seven of ten such patients will live out their lives with their limbs intact.

Grafts failed early due to technical problems involving the distal anastomosis or poor "runoff." Late failures were often the result of rather diffuse fibrotic hypertrophy of the vein wall. Occasionally, however, the fibrotic thickening of the vein wall was limited to a single location allowing simple patch repair and continued patency. Graft patency is unequivocally shown by palpation, as the grafts lie in the subcutaneum and are easily felt, particularly in the lower leg.

TABLE 1.—*Graft Site in 100 Femoral Tibial Grafts*

Anterior tibial	40
Posterior tibial	25
Dorsalis pedis	20
Peroneal	15

Figure 1.—An ideal candidate for posterior tibial bypass graft.

TABLE 2.—*Age Distribution of Patients*

Age	*Patients*
41-50	3
51-60	12
61-70	23
71-80	35
81-90	16
91-100	1

TABLE 3.—*Duration of Follow-up in Cases of Successful Revascularization*

30 days→1 yr.	21
1-2 years	13
2-3 years	12
3-4 years	10
4-5 years	6
5-6 years	2
6-7 years	4
	68

Discussion

Stimulated by the report of Garrett[1] in 1966, we began to use the distal bypass for severely diseascd extremities that would otherwise be subjected to amputation. We have been well satisfied with limb salvage and respectable patency rates, and find that this is now our most frequent operation in the leg below the groin. Our long-term results are quite similar to those of Tyson,[2,3] and we agree with him that it appears the preferred operation over bypass to the isolated popliteal segment. The latter may not salvage the limb due to obstruction distal to the anastomosis, and uses one source of vein graft if it is not effective.

We feel that the subcutaneous position of the graft is a definite advantage. It avoids bone removal or blind tunneling through the interosseous membrane; the former traumatizing a marginal limb unnecessarily and the latter lending itself to hemorrhage or graft kinking. Perhaps such techniques account for the lower patency rate noted by Imparato.[4]

The subcutaneous route has the additional late advantage of allowing auscultation and palpation of the graft in its entirety. One may easily then detect early reduction of pulses or bruits, indicating progressive graft stenosis from hypertrophy of the vein wall. The lesion can then be shown arteriographically, and simple repair can often be done under local anesthesia.

Meticulous technique and attention to the details outlined will allow successful vein grafting to 1.5 to 2 mm distal vessels. Though increments of additional flow may not be large, they are directed to the most distal portions of the compromised limb (Figure 2). Pain at rest disappears immediately following successful operation, and pregangrenous digits recover rapidly (Figure 3). Local debridement and minor amputation may then be done as necessary (Figure 4). Though early graft failure required amputation, some of the later failures maintained the healing promoted by the graft during its patency. When measured against a 20-percent to 30-percent operative mortality from major amputation, and the well recognized poor rehabilitation record of such patients, this procedure seems well worthwhile.

When presented with a problem of gangrene and severe ischemia secondary to severe obstructive disease in the popliteal vessels and below, one's options for therapy are limited. One either carries out an amputation below the knee or above the knee, or attempts reconstruction. We feel our success with femoral tibial bypass grafting indicates that reconstruction is the preferable procedure.

Figure 2.—A dorsalis pedis bypass graft with good foot filling.

Figure 3.—Typical lesions responding to this type of graft (same patient).

Conclusion

Femoral tibial vein grafting carries a small risk, is frequently successful in avoiding amputation and results in a useful extremity for the duration of the patient's life.

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Figure 4.—Well-healed very minor local amputations after a peroneal bypass graft.

Refer to: Carmel R: The laboratory diagnosis of megaloblastic anemias (Medical Progress). West J Med 128:294-304, Apr 1978

The Laboratory Diagnosis of Megaloblastic Anemias

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The diagnostic approach to megaloblastic anemia involves four usually sequential steps. The first step, recognition of megaloblastosis, requires attention to altered blood cell size and morphology. These changes may sometimes be subtle or masked. The cornerstone of the second step, identification of the specific vitamin deficiency, is assay of serum vitamin B_{12} and folic acid levels, although they may occasionally be misleading. The third step, identification of the specific disease entity responsible for the vitamin deficiency, generally revolves around tests of absorption and gastric function. The fourth step, reevaluation after replacement therapy, is often not thought of as a diagnostic step but carries important diagnostic implications and is sometimes the only way in which coexisting abnormalities can be unmasked and identified.

THE READY AVAILABILITY of vitamin assays has greatly simplified the diagnosis of megaloblastic anemias. However, the identification and therapy of vitamin deficiency both now appear so easy that the approach to megaloblastic anemia has come to be routine and occasionally even careless. Therefore, for example, a review of patients with vitamin B_{12} deficiency who were admitted to a Midwestern, university-affiliated, voluntary hospital over a four-year span showed incomplete investigation or incorrect diagnosis in approximately a third of cases in which the vitamin deficiency was identified by assay (unpublished data). A common error was to automatically label all cases of vitamin B_{12} deficiency as pernicious anemia, usually without resorting to a Schilling test but in several instances even when Schilling test results were incompatible with such a diagnosis. In this setting, significant and specifically treatable causes such as ileitis, intestinal bacterial overgrowth and sprue were sometimes not diagnosed. While management of folic acid deficiency in the same population was not similarly analyzed, folate-deficient patients rarely received further studies by their physicians for malabsorption or other diseases. They were simply given folic acid supplementation.

Perhaps more serious is the recent documentation that managing physicians often disregard

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evidence of possible vitamin deficiency uncovered by assays that they had themselves requested.[1] I have encountered this phenomenon frequently also, particularly if the assay result was not extremely low. Unfortunately, in a few cases the deficiency was thereby allowed to progress, sometimes to significant neurologic disability in the case of vitamin B_{12} deficiency.

The purpose of this review is to outline the armamentarium available for the optimal laboratory diagnosis of megaloblastic anemia, with emphasis on problems in interpreting results and on causes of misleading results. Well-established, reasonably accessible laboratory tests will be presented, as well as several other tests deserving wider attention. Since laboratory errors are inherent in any procedure, only common errors will be mentioned.

The diagnostic approach to megaloblastic anemia can be divided into four usually sequential steps.

1. Recognition of Megaloblastosis

Blood count and morphology usually establish the diagnosis of megaloblastic anemia. Occasionally, however, the picture may be modified or mild, and recognition may depend on active search for subtle morphologic changes. In general, the severity of megaloblastic morphologic abnormality is proportional to the severity of the anemia, and early megaloblastosis may manifest only very mild changes.[2-4] Consequently, 6-lobed neutrophils may be absent, and only an increase of 4-lobed or 5-lobed neutrophils may be evident.[2] Partially or incorrectly treated megaloblastosis may also look relatively normal morphologically, although Herbert[5] has stated that incorrectly treated megaloblastosis never looks completely normal.

A normal, or even low, mean corpuscular volume (MCV)—often resulting from microcytes coexisting with macrocytes—and masking of abnormal red cell morphology in bone marrow and peripheral blood is not unusual with coexisting iron deficiency[2,6,7] though white cell changes are not thus masked. However, the MCV is otherwise a valuable screening tool and can occasionally uncover megaloblastosis in a patient whose hemoglobin level is still normal. Of course, macrocytosis occurs in nonmegaloblastic states also, but examination of cell morphology is often sufficient to differentiate those from megaloblastosis.

TABLE 1.—*Usual Serum and Red Cell Assay Results in Vitamin B_{12} and Folate Deficiency States*

Serum Vitamin B_{12}	*Serum Folate*	*Red Cell Folate*	*Status*
N	N	N	Normal
N	↓	N	Normal,* or early folate deficiency
N	↓	↓	Folate deficiency
↓	↓	↓	Folate deficiency, or combined folate and B_{12} deficiency
↓	N-↑	↓-N	Vitamin B_{12} deficiency

N = normal levels; ↓ = low levels; ↑ = elevated levels

*But usually with recent poor dietary intake.

Megaloblastic changes found in erythroleukemia, various acute and chronic leukemias, and some refractory anemias, and with antineoplastic drugs, may occasionally be impossible to differentiate from vitamin B_{12} or folate deficiency by morphology alone. The white cell changes may tend to be less classical (and in the leukemias and refractory anemias may be absent) and polyploidy may be more prominent in the conditions not associated with vitamin deficiency, but firm data on these aspects are lacking. It has also been suggested that vitamin-deficient megaloblasts tend to have a clockface chromatin pattern which is not seen in megaloblasts in some other conditions.[8]

Neutrophil hypersegmentation has been reported in iron deficiency[9,10] and renal failure.[3] Whether subtle folic acid or vitamin B_{12} abnormalities in fact coexisted in most such cases is unsettled. Congenital neutrophil hypersegmentation has also been described[11,12] and may possibly occur in 1 percent of the population.[13] Conversely, it has been claimed that neutrophil hypersegmentation may not necessarily accompany folate deficiency in pregnancy[14] and rare patients with the Pelger-Hüet anomaly presented with 3-lobed or 4-lobed neutrophils rather than 6-lobed ones when megaloblastic.[15]

2. Identification of the Specific Vitamin Deficiency

The development of specific vitamin assays has greatly simplified matters because vitamin B_{12} and folic acid deficiency can be differentiated neither morphologically nor, often, clinically. However, serum levels do not always reflect body stores and are affected by many factors. Further confusion may result from the interactions between serum vitamin B_{12} and folic acid levels which

TABLE 2.—*Misleading Serum Folate Results**

Misleadingly Low Levels

Apparently normal persons.[17]

Poor dietary intake, without actual folate deficiency.[4,18]

Improper handling of blood sample (such as storage without freezing).

Drugs affecting assay: antibiotics,†[19-23] 5-fluorouracil,†[24] and possibly others.

Drugs not affecting assay:‡ acetylsalicylic acid,[25,26] alcohol,[27] ? oral contraceptives (see reference 28 for review).

Abnormality of serum folate-binding proteins:§ may give low results in pregnancy, oral contraceptive use, uremia and the like, with some radioassay systems but not others.[29,30]

Radioisotopic contamination of serum§ (for example, tracer injection for gallium or technetium scans).[31]

Misleadingly Normal or Raised Levels

Ingestion of folate-rich food[13] or vitamin supplementation.

Hemolysis of blood sample (red cell folate content greatly exceeds serum content).

Coexisting vitamin B_{12} deficiency[16,32] ("methyltetrahydrofolate trap" hypothesis,[16] vitamin B_{12}-dependent entry of folate into red cells[33]).

Disturbances in folate metabolism due to some drugs.[34]

Inborn errors of folate metabolism.[35]

Presence of methotrexate in serum.§[24,36]

*This information has been established for microbiological assay. Unless otherwise specified, it is assumed to be true for radioassay results also, but in some instances that assumption is untested.

†True for microbiological assay only.

‡The mechanisms of the drug effects are unknown, nor does true folate deficiency apparently result.

§True for radioisotopic assay only.

reflect in good part their metabolic interactions.[16] Sometimes overlooked too is the coexistence of both vitamin deficiencies. Therefore, determination of both vitamins simultaneously is often desirable. Table 1 shows the usual results of this approach and illustrates the occasional usefulness of red cell folate assay. Nevertheless results can obviously be inconclusive even with all three tests combined.

Serum Folate

The possible pitfalls in interpreting serum folate results are outlined in Table 2. Most of the accumulated experience has been with the microbiologic assay, the most common using Lactobacillus casei.[20] Because of the cumbersomeness of microbiologic assay and the inhibitory artifact induced by antibiotic therapy, many radioisotopic assays have been developed and marketed commercially as kits. Unfortunately, great differences exist among the isotopic methods, and many clinical laboratories have prematurely adopted and even modified kits without adequate testing.[37] The effect and significance of many variables remains controversial, and sufficient experience in comparing results to the standard microbiologic assay and to clinical data is lacking. Nevertheless, while the routine clinical use of folate radioassay is regrettable, the ultimate advantage of a reliable isotopic assay is clear.

The microbiological assay too is subject to many technical variables and results differ among laboratories.[32,38] In fact, in some cases the "falsely" low radioisotopic assay folate level due to serum folate binder abnormality may possibly reflect the true folate status more accurately than does the normal microbiologic assay level.[29] The current status of radioisotopic folate assay has been recently reviewed.[37,39]

It bears emphasizing that low serum folate levels need not, and often do not, mean actual folate deficiency and should be interpreted cautiously. Low levels have been found in apparently healthy control subjects.[17] Too, an early rapid fall in serum folate, appearing not to reflect true depletion of body stores, has been described in subjects on a folate-poor diet.[4,18] The mechanism for the fall appears to be the cessation of exchange between tissue stores and absorbed folate, and may at least partially explain the unusually great incidence of low serum folate levels in patients in hospital.[32] Such patients apparently require only reinstitution of a normal diet, but will progress to true folate deficiency if the poor diet is continued. Identifying the level of depletion may sometimes be difficult, and much obviously depends on how one chooses to define deficiency.

Red Blood Cell Folate

Red cell folate assay usually reflects tissue stores more accurately than does serum assay,[32] is less subject to influence by extraneous factors, and correlates with severity of anemia and megaloblastosis whereas serum folate does not.[40] Its greater specificity may be particularly useful when the existence of megaloblastosis is in question. An additional benefit is its helpfulness even after therapy has been started—thereby flooding the serum with folate—in the few days before folate-repleted cells are released from bone marrow in significant numbers. Because almost 10 percent of all serum specimens submitted for assay to my laboratory were drawn after the patient was given folic acid (unpublished data), this benefit may have great clinical utility. Obviously, too, samples

need not be obtained in the fasting state. Finally, antibiotic use has little effect on red cell folate assay.[21]

Table 3 outlines the various problems of evaluating red cell folate levels. The chief drawbacks of the test are its nondiscrimination between folate and vitamin B_{12} deficiency[40] due to the apparent dependence of folate entry into cells on vitamin B_{12},[33] and to its insensitivity to very early deficiency states.[4] The former drawback may be minimized by calculating red cell-to-serum folate ratios, which should be normal or high in folate deficiency but low in vitamin B_{12} deficiency,[40] but such ratios obviously require assay of both red cells and serum. As with serum folate, radioisotopic red cell folate assays are being developed[39,42,43] but are not fully tested yet.

Serum Vitamin B_{12}

Serum vitamin B_{12} is assayed by radioisotope dilution almost universally now. Results are comparable to microbiologic assay results, although slightly lower values have been reported with the latter assay, particularly in patients with folate deficiency and after gastrectomy.[44] It is not clear which result is "correct," and comparisons have suggested that the microbiologic assay identifies vitamin B_{12} deficiency more reliably.[45] A recent preliminary report[46] suggests that falsely-normal radioassay results may occasionally occur in vitamin B_{12} deficiency where microbiologic assay gives appropriately low values. Hall[47] has observed occasional falsely normal radioassay results also, as have I, but also mentions occasional falsely low vitamin B_{12} radioassay results where microbiologic assay levels are normal. The numerous published versions of the radioisotopic assay attest to the fact that an ideal technique does not yet exist. Many commercial kits have been marketed. Several of them unfortunately give higher results than others.* Therefore, 330 pg per ml is the lower limit of normal with some kits, whereas over the years microbiologic and most radioisotopic assays have established 150 to 200 pg per ml as the lower limit. The possible confusion resulting from this disparity is both obvious and deplorable. (I have recently seen a case where vitamin B_{12} deficiency was overlooked because of just this problem). Furthermore, each laboratory must establish its own range of normal values even when using commercial kits and not rely on manufacturers' claims (see last sentence of footnote).

Table 4 lists the possible interpretive errors with serum vitamin B_{12} levels. As with folate, serum levels only indirectly reflect body stores of vitamin B_{12} and its metabolic and transport sufficiency. A particularly important problem is that

TABLE 3.—*Misleading Red Cell Folate Results*

Misleadingly Low Levels

More than half of patients with vitamin B_{12} deficiency.[40]
Improper handling of specimen.
? oral contraceptives (see reference 28 for review).

Misleadingly Normal or High Levels

Early folate deficiency.[4]
Blood transfusion.
Significant reticulocytosis (since reticulocytes are relatively richer in folate than older cells).[16,40]
Iron deficiency.[41]

TABLE 4.—*Misleading Serum Vitamin B_{12} Results*

Misleadingly Low Levels

Folate deficiency.[49-51]
Pregnancy, near term[50,52,53]—particularly seen with microbiologic assay.[54]
Drugs: oral contraceptives,[55]
large amounts of vitamin C (probably by affecting assay).[56]
Idiopathic: aplastic anemia,[57] multiple myeloma,[58-60] cancer.[61]
Poor dietary intake in vegans (without true deficiency).[62]
Transcobalamin I deficiency.[63]
? Iron deficiency.[50,64]
? Old age.[65-67]
Artifact of radioassay.[47]
Contamination of serum with other radioisotopes in patients undergoing scans and uptake studies.[31]

Misleadingly Normal or Raised Levels

Vitamin administration before blood drawing.*
Artifact of radioassay.[46,47]
Serum vitamin B_{12}-binding protein abnormality coexisting with vitamin B_{12} deficiency: chronic myelogenous leukemia,[68,69] ? polycythemia vera.[70]
? Liver disease.[71]
Transcobalamin II deficiency.[72,73]
The generally higher results with some assay kits may be misinterpreted (must know normal range for the assay used).†

*Manufacturers of kits giving the higher results include Pharmacia Laboratories Inc., Piscataway, N.J. (Phadebas B_{12} Test) and Diagnostic Biochemistry Inc., San Diego, Calif. The more usual normal range is claimed for kits made by RIA Products Inc., Waltham, Mass.; Diagnostic Products Corp., Los Angeles Calif.; Clinical Assays Inc., Cambridge, Mass.; Schwartz-Mann, Orangeburg, N.Y.; Bio-Rad Laboratories, Richmond, Calif., and Curtis-Nuclear, Los Angeles, Calif. However, one study[48] reports that the last-named kit produced higher results than stated by the manufacturer.

*However, this is not as common as with folate since oral administration usually has no significant effect except in the rare patients with dietary vitamin B_{12} deficiency. I have found vitamin B_{12} injection to have contaminated at least 2.5 percent of sera submitted for vitamin B_{12} assay (unpublished data).

†For example, vitamin B_{12} assays for the Los Angeles County-University of Southern California Medical Center have in the past few years been done by several different laboratories, and three distinctly different normal ranges have therefore been operative at one time or another. A level of 150 pg per ml could be normal, borderline or clearly low, depending on the assay in use.

folate deficiency causes a decrease in serum vitamin B_{12} level in approximately half the cases,[49-51] sometimes to a level in the deficient range. While coexisting vitamin B_{12} deficiency has been suggested in some of these cases by *in vitro* studies,[74] the vitamin B_{12} level usually rises spontaneously following folate therapy alone.[49-51] Consequently, it is often difficult to establish whether a low serum vitamin B_{12} level in a folate-deficient patient represents a secondary phenomenon or coexisting true vitamin B_{12} deficiency. The problem then must be resolved by repeating vitamin B_{12} studies shortly after giving folic acid alone, or by assaying urine for methylmalonic acid. In my laboratory, 8 percent of patients with low serum folate had low levels of vitamin B_{12} also (unpublished data).

Urinary Methylmalonic Acid Excretion

In view of the occasional unreliability of serum vitamin B_{12} levels, determination of methylmalonic acid excretion may sometimes be clinically useful. This test would probably have wider utility were it more readily available and less demanding technically. Excretion of this intermediate is elevated in vitamin B_{12} deficiency but not in folate deficiency,[75] though oral loading with valine or isoleucine may sometimes be required to stress the metabolic pathway.[76] Furthermore, excretion results often remain abnormal for some time after vitamin B_{12} therapy,[77] making the test diagnostically useful in inadvertently treated patients. However, abnormal excretion also occurs in children with methylmalonic aciduria, a rare inborn error of metabolism, one variety of which is vitamin B_{12}-responsive,[78] and has been reported in advanced cirrhosis[79] and in a few elderly persons.[80] Misleadingly normal results in vitamin B_{12}-deficient subjects occur sometimes even with valine or isoleucine loading,[81] a reflection of the somewhat limited sensitivity of the procedure.

Other Tests

Beyond the above tests, few others are clinically useful. Red blood cell vitamin B_{12} assay is not generally available and lacks specificity;[82] low levels are encountered in folate deficiency,[83,84] iron deficiency[85] and polycythemia vera,[83,86] in addition to vitamin B_{12} deficiency.

Urinary excretion of formiminoglutamic acid is increased in folate deficiency[87] but is also increased in vitamin B_{12} deficiency.[88] This lack of specificity combined with its inconvenience makes the determination of urinary excretion of formimino-glutamic acid a test of limited clinical applicability.

The "deoxyuridine suppression" test[89,90] has been advocated as a very sensitive test of megaloblastosis, which identifies depletion, transport abnormality or metabolic block of either folate or vitamin B_{12}. Suitable *in vitro* maneuvers can frequently identify the specific defect. However, the test involves *in vitro* bone marrow culture, and is therefore only of research interest currently. Furthermore, coexisting iron deficiency can produce falsely normal deoxyuridine suppression,[91] much as red cell morphology can be masked in such a situation.

Even with the availability of the many laboratory tests mentioned above, evaluation of hematologic response to specific therapy with vitamin B_{12} or folic acid[5] may occasionally be clinically useful in some patients. Though the therapeutic trial is not necessary or feasible in most cases, its diagnostic validity requires the use of minimal doses of the specific vitamin to avoid the well-known response of vitamin B_{12} deficiency to massive doses of folic acid and to a lesser extent vice versa.

3. Identification of the Specific Disease Entity

Once the deficient vitamin has been identified, the underlying disease must be sought. The differential diagnosis has been well covered in many reviews[92-94] and textbooks, and is outside the scope of this discussion. Therapy can usually be started without interfering with this part of the evaluation, though certain precautions must be observed (see below).

Vitamin B_{12} Deficiency

Attention is directed primarily at establishing intrinsic factor lack (usually pernicious anemia) versus intrinsic factor ineffectiveness (usually intestinal disorders). Dietary deficiency is rare, though not unheard of, in the United States.[5,94] Even when the diet is unequivocally vitamin B_{12}-deficient, coexisting absorptive abnormality should still be considered since even vegans do not usually develop overt vitamin B_{12} deficiency.[95,96]

Gastric studies. Direct assay of gastric juice for intrinsic factor content is conceptually the ideal test. However, this assay is not widely available, even though it is a relatively simple, rapid method.[97,98] Its unavailability is particularly re-

TABLE 5.—*Misleading Results of Immunologic Assay for Intrinsic Factor Content in Gastric Juice*

Misleadingly Normal Results
Low intrinsic factor secretion which, though detectable, is insufficient for maintaining normal vitamin B_{12} absorption.[99]
Steroid therapy.[100-103]
Nonfunctional, but immunologically detectable, intrinsic factor molecule.*[104]
Misleadingly Abnormal Results
Incomplete gastric juice collection (most commonly improper placement of gastric tube or inadequate suctioning).
Failure to stimulate with histamine, betazole or pentagastrin.[105]
Improper processing of sample—for example, delay in depepsinizing sample may destroy intrinsic factor.[97]
Diminished amounts of intrinsic factor are occasionally found in patients who nevertheless absorb vitamin B_{12} adequately.[99]
Intrinsic factor secretion may be decreased secondarily in malabsorption syndromes such as sprue.[106-109]

*Can be identified by *in vitro* tests of mediation of vitamin uptake by gut mucosa.

grettable since patients with megaloblastic anemia often undergo gastric analysis anyway for the much less diagnostically specific purpose of determining gastric acid secretion. Intrinsic factor assay could decrease or eliminate the need for subsequent exposure of many such patients to the radioactivity of absorption tests. Possible artifacts of the assay are presented in Table 5, the most common being related to inadequate patient preparation and specimen collection.

Testing acid secretion, long a part of the evaluation of pernicious anemia, is not a specific test since achlorhydria often occurs in patients without pernicious anemia, particularly in elderly patients. As an illustration of its potential to mislead, in 28 consecutive *vitamin B_{12}-deficient* patients with achlorhydria I found five in whom adequate amounts of intrinsic factor actually were secreted and who therefore did not have pernicious anemia (unpublished data). Furthermore, reversible gastric atrophy has been reported to result from vitamin B_{12} deficiency itself[110] and from malabsorptive disorders.[106,107,109] Therefore, if gastric intrinsic factor assay is available, testing for acidity is an unnecessary procedure in evaluating vitamin B_{12} deficiency. However, because intrinsic factor assay generally is not available, determination of acid secretion is useful as a confirmatory but never as a diagnostic test. Exceptions to the rule that normal acid secretion rules out pernicious anemia include the rare entity of congenital pernicious anemia[111,112] and patients with adult pernicious anemia receiving steroids.[101,102]

Radioactive vitamin B_{12} absorption tests. The most commonly used of the various types of tests available is the Schilling test.[113] If properly done and analyzed, these tests are reliable. Reliability may be further enhanced by combining the Schilling test with plasma determinations of absorption.

However, a result indicating an intestinal absorption defect may be misleading since it is often a transient complication of pernicious anemia itself.[114,115] Furthermore, vitamin B_{12} deficiency can decrease absorption of other substances also.[114,115] Usually such malabsorption is quickly reversible but occasionally the Schilling test must be repeated after several months of vitamin B_{12} therapy. Nevertheless, delaying the Schilling test for this reason more than a few weeks is probably not necessary in most cases. It is also worth interjecting that while the prolonged reversible intestinal defect has been generally ascribed to vitamin B_{12} depletion of the intestinal cells, this explanation may not be entirely correct. Bone marrow normalization with therapy occurs within a few days, and intestinal cells have equally, if not more, rapid turnover. Therefore, if the absorptive defect takes months to reverse, mechanisms other than vitamin B_{12} deficiency per se may be implicated. For example, Lindenbaum and associates[115] found bacterial overgrowth requiring antibiotics in two such cases of pernicious anemia with prolonged vitamin B_{12} malabsorption. To further complicate matters, Brody and associates[116] found pernicious anemia and various primary intestinal diseases coexisting independently in several patients; in those cases the malabsorption was not transient. A much less common interpretative problem may be one arising in Diphyllobothrium latum infestation, where the abnormal Schilling test may or may not be correctable by exogenous intrinsic factor.[117] Obviously, being able to rule pernicious anemia in or out by examining gastric secretion of intrinsic factor by direct assay would be invaluable in the various situations mentioned above. However, as long as intrinsic factor assay remains generally unavailable, the Schilling test is still the cornerstone in investigating the cause of vitamin B_{12} deficiency despite its artifacts (Table 6).

Some question has been raised about the physiologic validity of an absorption test using crystal-

line cyanocobalamin rather than food vitamin B_{12} and of testing in the absence of the gastric stimulation normally occurring with food ingestion.[96,137-139] Modifications have therefore been proposed to more closely simulate the actual digestive and absorptive process[137-140] but a definitive answer is not available. These problems may be particularly pertinent in chronic pancreatitis,[121,122] postgastrectomy states[137,139] and gastric achlorhydria.[96,139]

Various technical modifications of the standard Schilling test have been introduced, but should be adopted cautiously. One such modification, the use of intrinsic factor in capsules, has been recently reported to give low results.[141] A commercial kit now also allows the simultaneous performance of the Schilling test with and without intrinsic factor by using two different cobalt isotopes,[142] but raises not only the question of exchange between the two simultaneously given doses of vitamin B_{12} but also of a possible 25-fold increase in radiation dose from the cobalt 58 isotope.[143] This radiation plus the unnecessariness of a second test in the many patients who turn out to have normal absorption without intrinsic factor probably outweigh any advantage in time saved that the test provides.

TABLE 6.—*Misleading Schilling Test Results*

Misleadingly Normal Results

Contamination of urine by other radioisotopes or by feces containing unabsorbed radioactive vitamin B_{12} (such as due to diarrhea, especially in women).

Patients with pernicious anemia taking steroids.[100-103,118]

Misleadingly Low Results

5 percent or more of normal subjects may have abnormal results.[119,120]

Vitamin B_{12} deficiency may produce transient malabsorption pattern.[114,115]

? Chronic pancreatitis.*[121,122]

? Folate deficiency.[123,124]

Drugs:† para-aminosalicylic acid,[121,122] colchicine,[127] neomycin,[128] phenformin,[129] metformin,[130] anticonvulsants,[131,132] potassium chloride,[133] potassium citrate,[134] alcohol.[135]

Incomplete urine collection.

Renal failure[92]—may often be circumvented by extending urine collection period to 48 or 72 hours.[88]

Vitamin B_{12} injection within 24 hours preceding the test.[97]

Vomiting or diarrhea.

Omitted or inappropriately timed "flushing" dose of vitamin B_{12}.[5]

A defective intrinsic factor preparation.

? Serum vitamin B_{12}-binding protein abnormality.[136]

*Schilling test results are frequently abnormal in chronic pancreatitis but the question raised about this entity is whether or not the test abnormality reflects true malabsorption.

†These are misleading only insofar as the drugs are rarely taken long enough to cause vitamin B_{12} deficiency, even though they apparently cause true, though transient, vitamin B_{12} malabsorption. The effect of many of these drugs, as had been shown with metformin, is dose-related.

Alternatives to the Schilling test exist which, instead of measuring urinary excretion of radioisotope, determine radioactivity in plasma,[119,144,145] feces,[146] whole-body counting[147] or hepatic uptake.[148] These tests enjoy the advantages of not require "flushing" injections of vitamin B_{12} or urine collection, but are subject to many of the other problems listed in Table 6 for the Schilling test. Since most of these alternative tests are not widely used, their specific problems will not be considered. The only test that is clinically important is the plasma absorption test which is rapid and simple, and bypasses the need for patient reliability and compliance. However, it is subject to other technical sources of possible error, there is overlap between normal and abnormal results[149] and results may be falsely elevated if renal impairment coexists.[119] Nevertheless, the plasma absorption test appears to be useful as a supplement to the Schilling test, particularly since the two tests can be carried out concurrently with the same dose of radioactive vitamin B_{12}.

Due to the many unavoidable, minor variations in procedure—such as the actual dose of radioactive vitamin B_{12} given—it is particularly important for each laboratory to establish the normal range for their test as done by them, rather than relying on published normal ranges.

Serum antibodies. More than half of all patients with adult pernicious anemia have "blocking" (type I) antibody to intrinsic factor circulating in their blood streams.[150] Assay is simple[97] and clinically useful because presence of this antibody is virtually diagnostic of pernicious anemia. Falsely positive antibody results[151-153] are rare, but assay artifact may occur if serum is drawn less than 24 to 48 hours after vitamin B_{12} injection.[97] The sole drawback to this test is the fact that absence of antibody is diagnostically meaningless: nearly half of all patients with adult pernicious anemia and all patients with congenital pernicious anemia do not have circulating anti-intrinsic factor antibody.

Parietal cell antibody is frequently found in the serum of patients with the adult but not the congenital form of pernicious anemia,[154] but is totally nonspecific. The antibody is found in so many patients without pernicious anemia as to make the

test of doubtful value clinically, other than as an indicator of gastritis.[154] This test is therefore rarely helpful diagnostically.

Folate Deficiency

Determination of the cause of folate deficiency is more difficult than with vitamin B_{12} deficiency, and in fact is usually not even attempted. A major problem is the lack of a reliable, widely available test for folate malabsorption. The various methods, reviewed elsewhere,[155] include measuring serum folate levels or urinary excretion of folate following a standard oral dose and tests resembling the radioactive vitamin B_{12} absorption tests in which isotopic folates are given. All require great expertise in carrying out and in interpreting results. A diagnosis of folate malabsorption, if made at all, is therefore usually established only indirectly by showing the presence of intestinal disease. However, in all truly deficient patients without very obvious dietary cause of deficiency, further general investigation must be done for malabsorption. Drug effect or possibly increased utilization of folate (the last named, incidentally, has never been conclusively shown as a sole cause of folate deficiency) should also be considered.

4. Reevaluation After Therapy

This phase is unfortunately often neglected, especially in patients discharged from hospital shortly after institution of therapy. Correctly treated, uncomplicated megaloblastic anemia should respond fully, and the maximal reticulocyte response by seven to ten days is well known. Equally important, the hemoglobin level should return completely to normal within two months. It may also be useful to recheck the serum vitamin B_{12} level in a folate-treated patient if it was borderline or low initially. The serum vitamin B_{12} level should rise spontaneously in folate deficiency correctly treated with folate;[49] further decline suggests vitamin B_{12} deficiency which coexisted or was previously misdiagnosed as folate deficiency.[156]

Lack of proper reticulocyte and red blood count response indicates incomplete correction of deficiency as outlined above, or coexistence of other causes of anemia, most often iron deficiency, inflammatory disease or alcohol abuse. Since any suboptimal response therefore calls for reinvestigation in the patient, it is essential to follow each case carefully to determine that full response has occurred.

Conclusion

Megaloblastic anemia should be suspected in any patient with macrocytosis and is confirmed by peripheral blood and bone marrow morphology. However, morphologic changes may be subtle, especially in early vitamin deficiency or with coexisting iron deficiency.

Identification of the specific vitamin deficiency is usually accomplished by assay of serum levels even though these do not always reflect body stores. Assay for both vitamin B_{12} and folate should be done together in most cases regardless of which vitamin deficiency is suspected clinically. This is so because the serum levels of the two vitamins interact (for example, low serum vitamin B_{12} levels have been reported in 10 percent of folate-deficient subjects) and because in some patients, particularly those with malabsorption, deficiencies of both vitamins may coexist. Even excluding artifacts and laboratory error, the specific vitamin deficiency may sometimes be hard to establish. Misleadingly low serum levels are particularly common. Folate stores may be more reliably assessed by red cell folate assay, but low levels do not distinguish between folate and vitamin B_{12} deficiency; vitamin B_{12} status may also be assessed by urinary methylmalonic acid excretion. Both red cell folate and urinary methylmalonic acid excretion assays are particularly useful in patients seen shortly after "shotgun" therapy in whom morphology and serum vitamin levels are no longer diagnostically reliable.

Identification of the specific disease entity must be pursued once the specific vitamin deficiency is identified. Tests of vitamin B_{12} absorption are widely available and generally reliable. A major interpretive problem is the transient intestinal malabsorption, ostensibly due to vitamin B_{12} deficiency itself, which often accompanies pernicious anemia. Although absorption tests usually need not therefore be delayed beyond a few weeks, other approaches obviously may be useful. Direct assay of gastric juice for intrinsic factor, ideally the single best test for establishing or ruling out pernicious anemia, is unfortunately not widely available. Assaying for serum antibody to intrinsic factor is also a useful test because a positive result

in a vitamin B_{12}-deficient patient is virtually diagnostic of pernicious anemia.

Identification of the cause of folate deficiency is more difficult since tests of folate absorption are not widely available. However, in any patient with definite folate deficiency not obviously due to poor diet, studies should be done for malabsorption or other causes.

Reevaluation in patients after treatment has important diagnostic implications as well. If appropriate hematologic response has not occurred, reinvestigation is indicated.

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Use of Propranolol in Diabetic Patients

PROPRANOLOL CAN CAUSE a really severe problem in a diabetic patient, especially one taking insulin, [because it] can mask the symptoms of hypoglycemia. Physicians must watch carefully for this and warn diabetic patients about it if propranolol is to be used.

—A. RICHARD CHRISTLIEB, MD, *Boston*

Extracted from *Audio-Digest Internal Medicine*, Vol. 24, No. 11, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

Specialty Conference

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Refer to: Hoefs JC, Peters RL, Redeker AG, et al: Chronic hepatitis B—Interdepartmental Conference, University of Southern California School of Medicine and the John Wesley County Hospital, Los Angeles (Specialty Conference). West J Med 128:305-317, Apr 1978

Chronic Hepatitis B

Patient

JOHN C. HOEFS, MD*

THE PATIENT is a 29-year-old white man who was first admitted to hospital at the University of Southern California (USC) Liver Unit at John Wesley Hospital in June 1972 with fatigue, nausea, anorexia and jaundice which had lasted for ten days. He admitted to heroin addiction since 1970. He stated he had "acute hepatitis" on two previous occasions (October 1969 and June 1970), each time with jaundice and recovery without hospital admission. On both occasions he was seen by a physician (laboratory test results from the 1969 episode were later found to be serum bilirubin 10 mg per dl and serum glutamic oxaloacetic transaminase (SGOT) 1,250 Reitman-Frankel units). Physical examination in June 1972 disclosed only jaundice and a questionably palpable liver edge. The test for hepatitis B surface antigen (HB_sAg) was positive by counterelectrophoresis (CEP), subtype ay. The diagnosis was acute type B hepatitis and this was supported by liver biopsy findings and a normal wedged hepatic vein pressure (WHVP) measurement. The patient recovered symptomatically from the acute hepatitis but findings on hepatic biochemical tests have never subsequently returned to normal levels and the HB_sAg test has remained positive. In May 1973 a firm liver edge and spleen tip were palpated, prompting a repeat liver biopsy study and WHVP measurement (Table 1). In October 1973 there was a brief period of jaundice with the SGOT level rising to 780 Reitman-Frankel units. Trials of therapy with transfer factor (1974) and prednisone (1973 and 1977) seemed ineffective and there has been progression of disease to cirrhosis. The patient has been continuously icteric during the past year and, since December 1976, ascites and edema have been present requiring diuretic therapy.

On physical examination now, the patient is healthy appearing with mild scleral icterus, numerous vascular spiders, palmar erythema, palpable, firm liver and spleen, and minimal ascites and edema.

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Pathologic Findings

ROBERT L. PETERS, MD†

Examination of the liver biopsy specimen of June 14, 1972, taken two weeks after the onset of jaundice, showed an intact lobular architecture, each lobule was similar to its neighbor with respect to distribution and extent of hepatocellular changes. The perivenular hepatocytes were swollen. Poorly defined, serpiginous areas of hepato-

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ABBREVIATIONS USED IN TEXT

AVH = acute viral hepatitis
CAH = chronic active viral hepatitis
CEP = counterelectrophoresis
DNA = deoxyribonucleic acid
HAV = hepatitis A virus
HB_cAg = hepatitis B core antigen
HB_eAg = hepatitis B "e" antigen
HB_sAg = hepatitis B surface antigen
HBV = hepatitis B virus
IRS = impaired regeneration syndrome
PVH = persistent viral hepatitis
SGOT = serum glutamic oxaloacetic transaminase
SGPT = serum glutamic pyruvic transaminase
WHVP = wedged hepatic vein pressure

cytolysis were intermingled among the perivenular hydropic cells. Lymphocytic exudate was prominent, both in foci of hepatocytolysis and in portal areas where limiting plates were traversed. Portal areas were not widened and there was no increase in fibrosis (Figure 1).

Study of the second biopsy specimen, taken April 24, 1973, ten months later, showed that the lymphocytic exudative reaction was still prominent but irregularly patchy. There was no longer a predilection toward greater perivenular necrosis, instead there were small punched out areas of hepatocytolysis irregularly distributed throughout the lobules. In addition there was widespread Kupffer cell hyperplasia, and thin irregular strands of connective tissue extending from portal areas, as well as from small foci of hepatocellular destruction (Figure 2).

The third biopsy specimen, October 12, 1973, had complete disruption of the lobular architecture by cellular connective tissue invading poorly defined nodules of hydropic hepatocytes. The connective tissue was heavily infiltrated by plasma cells but there were only occasional foci of exudate within the parenchyma. By October 2, 1975, the liver was frankly cirrhotic with some continuing focal necrosis (Figure 3).

Discussion

About 85 percent of patients with clinically evident acute viral hepatitis recover completely and 1 percent die of the acute disease; in the remainder, some form of chronic liver disease develops. The risk of chronicity is much higher when the initial disease is subclinical.[1]

Diseases that clinically appear to be chronic may be separated into the following categories:

Figure 1.—Liver biopsy specimen of June 14, 1972, showing the changes of typical acute viral hepatitis. Note that the terminal hepatic vein **(left lower corner)** is surrounded by the greatest cell swelling and hepatocytolysis even though the parenchyma around the portal area **(midway between top and bottom near right margin)** are in some disarray (H&E reduced from ×63).

TABLE 1.—*Selected Test Results in Patient*

Date	Serum: Bilirubin (mg/dl)	Serum: Albumin (grams/dl)	Serum: Globulin (grams/dl)	Serum: SGOT (R-FU)	Serum: SGPT (R-FU)	Prothrombin (Percent)	HB_sAg (CEP)	
6/9/72	20.0	4.3	3.9	1,080	926	..	+	Biopsy No. 1 WHVP 4 mm of mercury*
4/23/73	0.8	3.9	4.5	55	40	..	+	Biopsy No. 2 WHVP 7 mm of mercury
10/5/73	11.8	4.1	4.5	780	650	62	+	Biopsy No. 3
1/10/74	1.2	3.9	5.8	147	124	..	+	WHVP 9 mm of mercury
10/25/75	1.9	3.2	5.9	134	61	82	+	Biopsy No. 4
12/9/76	5.8	2.9	4.5	176	62	39	+	..
7/28/77	7.2	2.6	5.5	209	66	36	+	..

R-FU = Reitman-Frankel units CEP = counterelectrophoresis WHVP = wedged hepatic venous pressure

Special studies: "e" antigen and anti-e both negative on 3/21/73 and 2/3/77.
Dane particle percent 0.6 and deoxyribonucleic acid (DNA) polymerase negative, October 1975.
Anti-core positive 2/3/77.

*Zero reference point for pressure measurement is the inferior vena cava.

- Those in which replication of hepatocytes is retarded to the point that the clinical course is greatly prolonged or the process is ultimately fatal after several months of illness.
- Those in which the etiologic agent remains in the liver.

The first condition, the *impaired regeneration syndrome* (IRS), which occurs predominantly in patients over forty years of age, is not truly a chronic progressive condition but a prolonged recovery reflecting the reduced capacity for hepatocyte regeneration that is commensurate with aging. The IRS generally persists less than a year, the patient either succumbing or recovering in that period. Histologically the IRS is often mistaken for a truly chronic form of hepatitis. There is generally confluent necrosis around the terminal hepatic vein. Portal areas are widened, often with bridging necrosis between adjacent portal areas and each lobule is similar to the next (Figure 4).[2] Usually if the liver biopsy specimen is taken about two months after the acute illness, continuing necrosis and exudate are quite diminished.[3] Cholestasis, particularly periportal cholestasis, is often striking (Figure 5). A key feature is the lack of evidence of a persistent etiologic agent.

Figure 2.—Biopsy specimen taken ten months later than that of Figure 1 showing that the focal hepatocytolysis is now randomly and irregularly distributed, the portal area **(upper right)** is raggedly widened. Columns of Kuppfer cells course through the liver (araldite, 2 microns, H&E reduced from ×105).

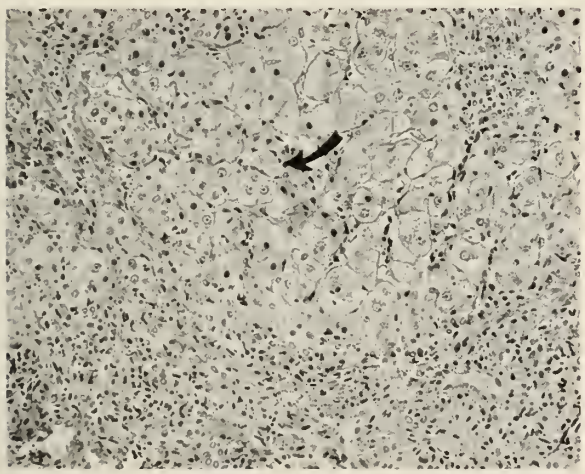

Figure 3.—By October 2, 1975, the liver was frankly cirrhotic. Note the irregular parenchymal nodule with a few foci of cuffs of lymphocytes **(arrow)** (araldite, 2 microns, H&E reduced from ×210).

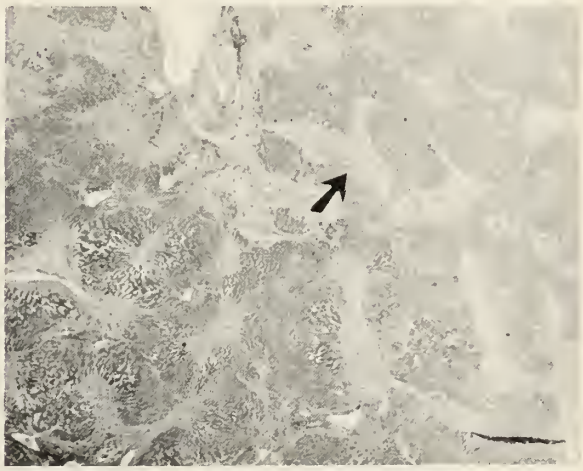

Figure 4.—Low power photomicrograph of liver of patient with failure of hepatocytes to regenerate two months after acute viral hepatitis. Note the straight hepatic cords radiating into the collapsed perivenular areas **(arrow)** (H&E reduced from ×20).

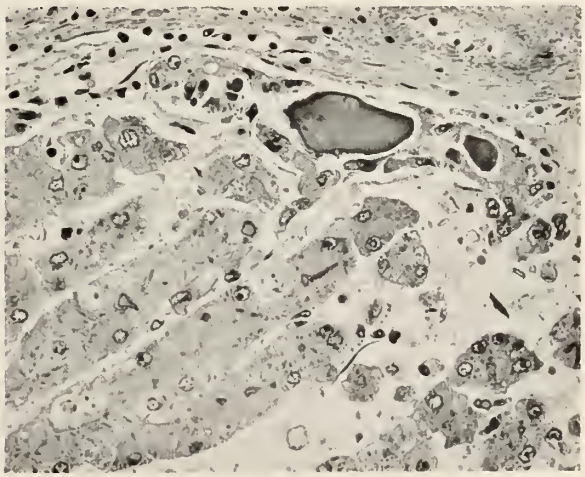

Figure 5.—Periportal cholestasis in impaired regeneration syndrome (H&E reduced from ×560).

True chronicity in which the etiologic agent is not disposed of, falls into two broad categories: (1) a form that is not progressive and (2) a form that is progressive.

Persistent viral hepatitis (PVH), the nonprogressive type of chronic hepatitis, is an asymptomatic condition following either clinically evident or subclinical infection. From its onset PVH is associated with meager biochemical and histologic alterations. With the passage of years, the changes become even more meager and blend into normalcy. For the first three to five years after acute disease, PVH is characterized histologically by uniformly hydropic hepatocytes, the cord-sinusoid pattern is lost resulting in a "cobblestone" configuration. There are occasional small punched-out foci of hepatocytolysis containing lymphocytes, but there is no infiltration of lymphocytes to form cuffs around hepatocytes (Figure 6). About half the patients have lymphoid hyperplasia in portal areas, usually this hyperplasia is sharply confined within the limiting plates. But if the patient is a chronic intravenous drug user, portal areas may be widened by inflammatory infiltrate and connective tissue that is apparently unrelated to the viral infection but is an expression of the reticuloendothelial reaction to inoculation of foreign material (Figure 7).

Slowly the above changes of PVH regress so that by three to five years the cord pattern becomes reestablished and the focal hepatocytolysis diminishes yet further. At about the same time, scattered peculiar bloated granular cells may begin to appear. These cells, the ground-glass cells of Hadziyannis, contain large amounts of HB_sAg and when present are regularly distributed throughout the biopsy specimen in PVH type B (Figure 8). Apparently PVH as described above does not progress to more serious forms of chronic liver disease.

A progressive form of chronic hepatitis type B, although less common, has been of greater clinical concern. The progressive lesion which is called *chronic active viral hepatitis* (CAH) type B may be further subdivided into a classical and a subclinical variety. The case that has just been discussed fits into the classical variety.

Acute viral hepatitis, at the height of disease, is characterized histologically by uniformity of involvement from one lobule to the next, and within one lobule by the perivenular accentuation

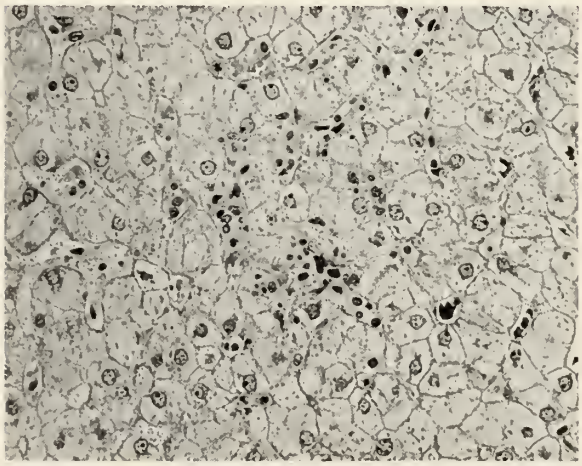

Figure 6.—Focal hepatocytolysis in biopsy specimen from patient with persistent viral hepatitis (H&E reduced from ×560).

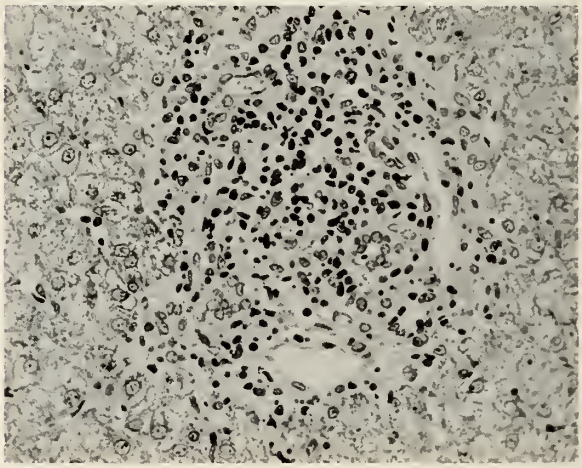

Figure 7.—Portal lymphoid hyperplasia, prominent in about half of biopsy specimens from patients with persistent viral hepatitis type B (H&E reduced from ×560).

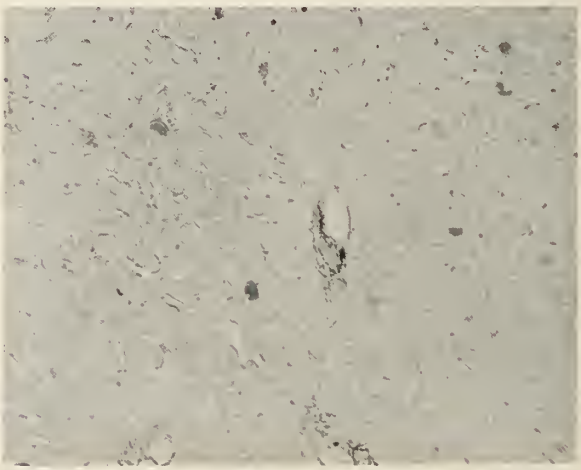

Figure 8.—Regular distribution of HB_sAg-positive cells (dark staining cells) in liver of patient with persistent viral hepatitis type B (Shikata-Orcein reduced from ×105).

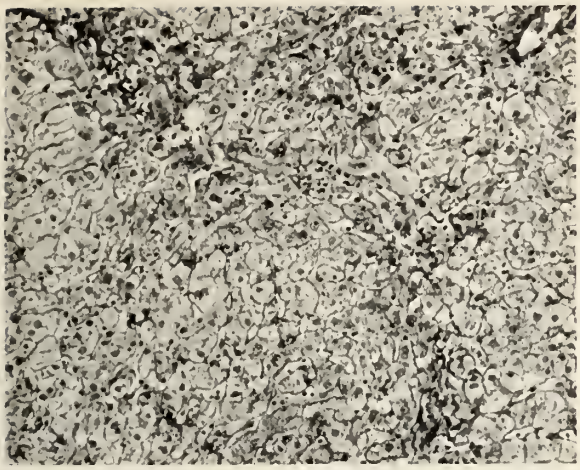

Figure 9.—1949 biopsy specimen from essentially asymptomatic patient showing bulging areas of parenchyma. By 1951 ground-glass cells could be found (araldite, 2 microns, H&E reduced from ×105).

of hepatocytolysis and cell damage pattern. The periportal hepatocytes are usually slightly hydropic with loss of the well-defined hepatic cord arrangement. The hepatocyte nuclei are unusually uniform with finely divided nuclear chromatin and prominent nucleoli. Portal areas may be minimally or heavily exudative but rarely feature increased amounts of collagen.

In contrast, in most patients with chronic active viral hepatitis, even in the very early stages, a perivenular orientation of maximal damage is not seen. Instead, focal hepatocytolysis and hydropic change may be irregularly distributed in the lobule. There may be subtle areas of regeneration within the lobules, and one lobule may differ sharply from another. Kupffer cell proliferation may be quite striking throughout the lobule in early stages of CAH. There is usually some increased deposition of collagen in portal areas even before portal widening develops.

Classical chronic active hepatitis B is the precursor disease of only a small percentage of patients in whom B-viral cirrhosis ultimately develops. Of 31 patients dying of B-viral cirrhosis at the John Wesley USC Liver Unit between 1962 and June 30, 1977, only six had a history of any earlier illness that could be recognized even in retrospect as either chronic active or acute viral hepatitis, and of 27 patients dying of hepatocellular carcinoma and B viral cirrhosis, only two had history of a hepatitis-like illness. The histologic changes taking place during the subclinical development of the coarsely nodular cirrhosis have been largely conjectural; however, some liver biopsy studies have been done on ostensibly well persons who have been found to have HB_sAg in their sera. Most of those in whom biopsy studies were done have had persistent hepatitis, some have had cirrhosis,[4] a few have had changes beyond those found in liver specimens from patients with persistent hepatitis. Livers of patients in the latter group have had poorly defined areas of larger, more hydropic hepatocytes bulging against smaller, more eosinophilic hepatocytes. The nuclei may be irregular and there may be areas with Kupffer cell hyperplasia, differing in extent from one lobule to the next. There is usually little necrosis or exudate (Figure 9). On the basis of serial study of a few such patients, it would appear that ultimately the bulging, hydropic areas become true nodules (Figure 10). Two important questions remain unanswered. One is whether or not the pattern we recognize as early subclinical CAH-B invariably progresses relentlessly to cirrhosis, and the second is if cases of PVH-B ever convert to subclinical CAH-B.

The patient presented above had clinical and pathologic features of classical active hepatitis with the ultimate development of B-viral cirrhosis. There was, however, a major unusual feature, the initial biopsy findings even upon review were indistinguishable from those found in acute viral hepatitis. In most patients with classical chronic active hepatitis, the liver biopsy specimen taken when the disease is first recognized clinically has pathologic changes differing somewhat from typical self-limited acute viral hepatitis.

Differential Diagnosis

ALLAN G. REDECKER, MD*

The patient presented today clearly has cirrhosis now as evidenced by the firm palpable liver, splenomegaly, ascites, low level of plasma albumin and a very reduced level of prothrombin activity. In addition, in this patient there has been continuing necrosis and inflammation since the initial type B infection in 1972 as evidenced by the liver biopsy material and the continuous elevations of the SGOT and SGPT. Therefore, in less than five years an episode of acute viral hepatitis (AVH) has progressed to clinically obvious cirrhosis.

Fortunately, most patients who suffer an acute infection with one of the hepatitis viruses recover

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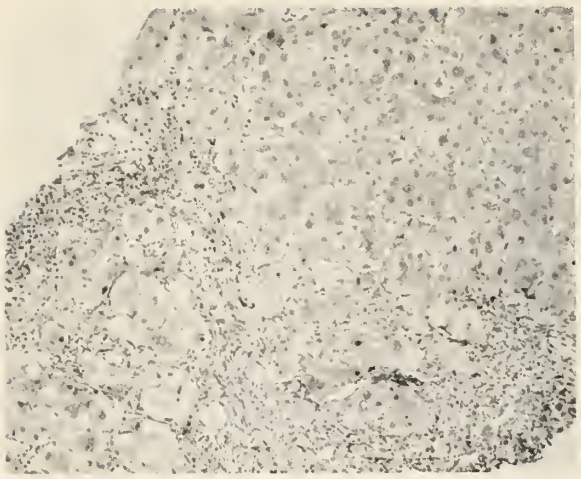

Figure 10.—Biopsy specimen (patient of Figure 9) taken in 1973 showing the subclinical cirrhosis (araldite, 2 microns, H&E reduced from ×105).

completely without any residual. Apparently there is no low term sequela at all following type A hepatitis. Chronic forms of hepatitis, however, follow infections with both type B and non-A non-B virus. Because of the availability of specific serological markers the most accurate long-term studies have been made in patients with type B hepatitis. It is customary to attempt to classify forms of chronic viral hepatitis into two categories. The purpose of this is to define two forms with very different long-term prognoses and to select patients for possible treatment. Unfortunately, not all patients fit easily into such discrete categories, at least not at all stages of their chronic disease. The most frequent chronic lesion is persistent viral hepatitis. In our experience this disorder is characterized by chronic or recurrent transaminase elevations with general good health and absence of recurrent or chronic jaundice. As with the histological features, PVH tends to be most active in terms of transaminase elevations early during the first months or years following the acute infection, then becomes quiescent. Therefore, if a patient has chronic hepatitis B antigenemia, he eventually evolves into a completely healthy HB_sAg carrier without any hepatic disease at all.

The other form of chronic hepatitis, chronic active hepatitis, is a lesion that has been variously defined, both in clinical and histological features. We prefer to consider CAH as a relentlessly progressive form of chronic hepatitis, leading virtually always to cirrhosis, but at a highly variable rate. In some instances the progression to clinical cirrhosis is very rapid, that is, it occurs in less than one year. In other patients, after an early period of rather pronounced activity (transaminase elevations and sometimes jaundice), the disease becomes quiescent. Further progression occurs at a slow and insidious rate over a great many years, resulting eventually in some complication of advanced cirrhosis (portal hypertension, hepatic failure, hepatocellular carcinoma). In some patients, periods of quiescence are periodically punctuated by bouts of necrosis and inflammation accompanied by clinical jaundice and high serum transaminase levels looking much like a de novo episode of acute hepatitis. Such an episode occurred (in October 1973) in the patient presented today. Interestingly, this patient had had two episodes of acute jaundice, each thought to be acute viral hepatitis with resolution before the episode in 1972. These multiple bouts of acute viral hepatitis observed in addicts do not seem to commonly eventuate in chronic hepatitis, the present case being an exception.[5] Neither does initially very severe AVH provide a common background for chronic hepatitis.[6] In patients who survive fulminant acute hepatitis, chronic hepatitis in any form rarely if ever develops.[6] On the other hand, as pointed out by Doctor Peters, initially mild (that it, anicteric) AVH must be the most common type of the acute infection leading to chronicity, since most patients with CAH do not have a history of initial acute hepatitis with jaundice. In a long-term follow-up study of patients with acute icteric type B hepatitis we found that in 3 percent CAH developed and in 7 percent PVH developed.[7]

For the clinician, the distinction between PVH and CAH can be a challenging task. Liver biopsy is certainly the mainstay of diagnosis. However, at times the histological features are not clear cut or the tissue specimen is inadequate. Three additional measurements can be useful in clarifying these situations. We have found the wedged hepatic vein pressure to be almost uniformly elevated in patients with histological features of CAH and not raised in patients with PVH.[8] This is a safe, minimally invasive procedure. Second, it is now clear that in cases of chronic type B hepatitis, there is usually a reciprocal relationship between the strength of the surface antigen reactivity (HB_sAg titer) and the severity of the chronic hepatitis.[7] Therefore, patients with CAH or cirrhosis commonly have persistently low HB_sAg titers, a feature seldom observed in patients with

TABLE 2.—*"e" Antigen in Chronic Type B Hepatitis: Correlation with Histological Type*

Type of Hepatitis	Number	"e" Positive	
		Number	Percent
PVH[11]	40	20	50
CAH	89	31	34.7
PVH[12]	22	15	68
CAH	20	8	40

PVH = persistent viral hepatitis
CAH = chronic active viral hepatitis

PVH or in asymptomatic carriers. Third, if the CAH has progressed to any degree of cirrhosis, a view of the surface of the liver during peritoneoscopy showing nodules or undulations is very informative.

In the patient presented today, there was raised WHVP since at least April 1973. HB_sAg was positive by the CEP technique at a dilution of 1:1 in April 1973, and at 1:4 in March 1977. These are low titers; in most patients with PVH there are titers of 1:16 or greater. Recently, reports have suggested that the presence of the "e" antigen in patients who are chronically HB_sAg-positive might favor the development of CAH rather than PVH or the asymptomatic carrier state.[9,10] Two studies, however, failed to find any support for this and in fact found the frequency of "e" antigen detected at some time during the course of chronic type B hepatitis to be slightly greater in patients with PVH than in those with CAH (Table 2).[11,12] This is consistent with the finding that "e" antigen is correlated with a high titer of HB_sAg as occurs in PVH and less frequently observed when the HB_sAg titer is low, as in CAH.

Serological Markers

MYRON J. TONG, PhD, MD*

There are at present three antigen-antibody systems that are associated with the hepatitis B virus.[13] There are (1) HB_sAg: anti-HB_s, (2) hepatitis B core antigen (HB_cAg): anti-HB_c and (3) hepatitis B "e" antigen (HB_eAg): anti-HB_e. In the HB_sAg: anti-HB_s system, three morphologic forms of HB_sAg, all with identical antigenic properties, have been identified by electron microscopy. One form is the Dane particle which is 42 nM in diameter and is considered to be the complete virion. The Dane particle consists of an inner core and outer surface antigen. Another form is a 22-nM in diameter spherical particle which probably represents excess viral coat material. The 22-nM particles have been purified by cesium chloride density gradient centrifugation and this material is currently being tested as a vaccine to the hepatitis B virus. The third morphologic form is tubular in appearance, is of variable length and has a diameter of approximately 22 nM. All of these morphologic forms are synthesized in the cytoplasm of the hepatocyte. Electron microscopic examination of the serum from the patient presented today showed that most of the viral particles were 22 nM in size. Dane particles were few in number and represented only 0.6 percent of the total number of particles present in his serum. The antibody to HB_sAg is designated as anti-HB_s. Anti-HB_s appears in persons who have recovered from acute hepatitis B infections and is considered to be the protective antibody. Hepatitis B immune globulin prepared from persons with high circulating anti-HB_s titers has been shown to confer passive immunity to most exposed persons.

The antigen in the HB_cAg: anti-HB_c system (core antigen) is located within the complete Dane particle. HB_cAg has not been identified in its free form in serum and its detection is dependent on disruption of the Dane particles by detergent treatment. HB_cAg contains a viral-specific deoxyribonucleic acid (DNA) polymerase enzyme which catalyzes the polymerization of exogenously added deoxynucleoside triphosphates.[14] Also within the HB_cAg is a circular, double-stranded DNA which is the genetic material of the hepatitis B virus (HBV). The HBV-specific DNA polymerase is a specific marker for the Dane particles and is presently considered to be the most sensitive indicator of viral infectivity. HB_cAg is found in the nucleus of the liver cell. Anti-HB_c is detected early in the course of acute type B hepatitis and is found in virtually all patients who have recently recovered from the disease. Anti-HB_c may be detected for up to two years after the initial exposure but decreases in titer thereafter.[15] This antibody is also found in all chronic HB_sAg carriers and patients with chronic liver disease due to hepatitis B and is therefore not a protective antibody. The tests for anti-HB_c and DNA polymerase are still research procedures and not available in most clinical laboratories.

HB_eAg ("e" antigen) was first described by Magnius and Espmark in 1972. HB_eAg is only detected in HB_sAg-positive persons. Recent studies

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have shown that there is a strong correlation between the presence of HB_eAg, DNA polymerase and Dane particles. Therefore, HB_eAg may be a useful indicator of viral infectivity.[12] In acute type B hepatitis, HB_eAg is detected early in the course of illness and disappears during the convalescent period. HB_eAg is also found in some asymptomatic HB_sAg carriers, as well as in some patients with either chronic active type B hepatitis, cirrhosis or HB_sAg-positive hepatocellular carcinoma. Therefore, HB_eAg does not appear to be related to either the chronicity or severity of the liver disease caused by the HBV. A recent study from our laboratory has shown that not only is HB_eAg found free in serum separately from Dane particles but also may be released after detergent treatment of Dane particle-rich preparations suggesting that HB_eAg is located between the surface and core antigens.[16] Anti-e is found in some HB_sAg-positive carriers as well as in some patients with chronic hepatitis. Whereas HB_eAg is an indicator of infectivity, there is some evidence that the presence of anti-e may denote noninfectivity. Okada from Japan reported that HB_sAg carrier mothers who were HB_eAg-positive transmitted hepatitis B to their unborn infants whereas infants from HB_sAg-positive carrier mothers with anti-e were free from HBV infection.[17] However, the significance of HB_eAg and anti-HB_e has not yet been clearly established. The serologic test presently available for the HB_eAg: anti-HB_e system is considered to be insensitive. Consequently, there are some patients such as our patient today who have neither HB_eAg nor anti-HB_e as measured by the technique of rheophoresis. A better understanding of HB_eAg: anti-HB_e should be forthcoming with the development of more sensitive methods for their detection.

Epidemiology

JAMES W. MOSLEY, MD*

This patient's epidemiologic history indicates that his first episode of acute viral hepatitis occurred in October 1969, following sexual contact with a woman with acute hepatitis. Her jaundice antedated his illness, but the interval between the two onsets is unknown. He began intravenous use of heroin early in 1970, and frequently shared the equipment for his injections. The latter practice was the presumptive mechanism leading to his second bout of acute icteric disease in June of 1970. He saw a private physician at the time of each of these bouts; he was not admitted to hospital for either.

His first admission to the Liver Unit was in June 1972, with self-injection of illicit drugs again the background for acute icteric disease. The test for HB_sAg was positive at that time and has remained so subsequently. Although it seems very likely that hepatitis B virus was responsible for the 1972 occurrence, that inference cannot be conclusively established with the serologic tests now available. It is possible that the chronic HBV infection was acquired at some previous time, with the June 1972 episode being due to another agent of human hepatitis. The exact time of infection is of little practical consequence in relation to the patient's subsequent course. I merely wish to point out that the occurrence of HB_sAg during acute viral hepatitis does not necessarily indicate that the particular episode is due to HBV.[18] If the patient continues to be HB_sAg-positive during subsequent observations, the time of infection, strictly speaking, is indeterminate. If he becomes HB_sAg-negative in convalescence, then the probability of antecedent HBV infection is exceedingly remote.

It is important for the physician attempting to make an etiologic diagnosis to realize that the epidemiologic history in individual cases is not a reliable means of identifying the virus involved. In the past, this particular patient's first illness would have been called infectious hepatitis because it followed close contact. His second acute episode would have been termed serum hepatitis because it followed percutaneous (parenteral) infection. The third, for which he was first admitted to the Liver Unit, would usually have been considered by most physicians as either a recrudescence of chronic type B hepatitis or a reinfection of HBV. We have found, however, that a history of self-injection of illicit drugs is given as frequently by patients with non-B hepatitis as by those with HB_sAg positivity.[19] In fact, in a more recently studied group, illicit self-injection was acknowledged by the same proportion of patients with serologically shown type A hepatitis as by those with non-A non-B disease.[20] We also know that HBV is transmitted by intimate contact.[21] We must, therefore, abandon the terms infectious and serum hepatitis, which have an epidemiologic as well as etiologic connotation in the minds of most physicians. Until a test for type A hepatitis moves from the research to the clinical laboratory,

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the practitioner can diagnose serologically only type B hepatitis. Unless the patient has a positive test for HB_sAg, sporadic cases should be classified as "viral hepatitis, type unknown."

This patient's first admission (June 1972) to the Liver Unit occurred during the time that an intensive epidemiologic study was being conducted by the Hepatic Epidemiology Laboratory (supported by grant 10586 of the National Institute of Allergy and Infectious Diseases). For the ten-month period from November 1971 through August 1972 there were 692 patients seen on the Liver Service at USC for whom the discharge diagnosis was viral hepatitis. Of these, 202 men and 75 women admitted self-injection of drugs on one or more occasions within the six months before onset of symptoms (Table 3). These patients were largely in their late teens and 20's but there were 36 men and 11 women who were in their 30's or older. By the counterelectrophoresis (CEP) method for HB_sAg used at that time, 55 percent of the men and 45 percent of the women had evidence of HBV infection. Subsequent experience with more sensitive methods, as well as assay for antibody to hepatitis B core antigen, has shown that CEP in a research laboratory underestimates the prevalence of *acute* HBV infection by no more than 5 to 10 percent.[20] Therefore, HBV has been responsible for slightly more than half of the cases in persons admitting self-injection of illicit drugs. The remainder represent a combination of type A hepatitis, acquired either by contact or percutaneously, and non-A non-B hepatitis.

The patient being discussed today was infected with an HBV strain having the **y** subdeterminant of the **d, y** pair. HB_sAg/**ay** strains have been predominant in cases of type B hepatitis associated with self-injection of illicit drugs in Los Angeles (Table 4), elsewhere in the United States and in other parts of the world.[22] There is no reason to believe that there is any intrinsic characteristic of /**ay** strains that would favor transmission among persons with a background of drug abuse. It seems much more likely that they occur because of the social closeness of persons in the drug culture, admission to which required the sharing of illicit materials as well as the equipment for their injection. Another striking aspect of the drug culture at that time was the extent to which social dropouts migrated from group to group within a city, from city to city within the United States, and from the United States to many other countries. Therefore, it is not surprising that one subtype characterizes this epidemiologic form

TABLE 3.—*Frequency of hepatitis B surface antigen positivity. Patients admitting self-injection of illicit drugs within six months before acute hepatitis. Liver Unit, USC School of Medicine, November 1971 through August 1972.*

	Men			*Women*		
		HB_sAg (+)			*HB_sAg (+)*	
Age Group	*Total Number*	*Number*	*Percent*	*Total Number*	*Number*	*Percent*
15-19	35	22	63	12	6	50
20-24	89	49	55	37	20	54
25-29	48	21	44	16	5	31
30+	36	20	56	11	3	27
Total	202	112	55	75	34	45

TABLE 4.—*Hepatitis B surface antigen subtypes. Patients admitting self-injection of illicit drugs within six months before acute hepatitis. Liver Unit, USC School of Medicine, November 1971 through August 1972.*

	HB_sAg (+) Men			*HB_sAg (+) Women**		
Age Group	*Number /ad*	*Number /ay*	*Ratio (pct:pct)*	*Number /ad*	*Number /ay*	*Ratio (pct:pct)*
15-19	1	21	5:95	..	6	NM
20-24	4	45	8:92	2	18	10:90
25-29	6	15	29:71	..	4	NM
30+	2	18	10:90	..	3	NM
Total	13	99	12:88	2	31	6:94

NM = not meaningful.

*Omits one patient whose HB_sAg could not be subtyped.

TABLE 5. *History of prior episode(s) diagnosed as viral hepatitis. Patients admitting self-injection of illicit drugs at any time in their lives. Liver Unit, USC School of Medicine, November 1971 through August 1972.*

	Admitted Illicit Self-Injection				*Denied Illicit Self-Injection**			
		Number of Previous Attacks				*Number of Previous Attacks*		
Age Group	*Total*	*One*	*Two*	*Three*	*Total*	*One*	*Two*	*Three*
15-19	56	9	..	..	60	1	1	..
20-24	135	16	4	1	116	7	..	..
25-29	71	11	5	2	79	4	..	..
30+	47	12	2	..	101	6	..	..
Total	309	48	11	3	356	18	1	..

*Omits 27 patients for whom a definite answer was not recorded.

of type B hepatitis. An analogy is the predominance of one subtype (usually /**ad**) within individual hemodialysis centers.[23]

It also seems worthwhile to comment upon the fact that this patient had three distinct episodes of acute hepatitis. Biopsy at the time of the third (June, 1972) showed no evidence of background chronicity, so that recrudescence of type B hepatitis seems an unlikely explanation. The first report of three bouts of acute disease was by Havens in 1956[24] and scattered others have been mentioned in the subsequent literature. The very large experience of our Liver Unit with addiction-associated disease in the late 1960's and early 1970's permitted documentation of three bouts in five patients and four episodes in six additional patients. Serologic study of selected patients with multiple episodes for markers of hepatitis A virus (HAV) and HBV showed no instances of reinfection by the same agent.[5]

Table 5 compares the frequency of undocumented previous attacks of icteric hepatitis (by history only) among persons admitting and denying self-injection of illicit drugs at any time in their lives (not just the six months before admission). Among 309 admitted drug users, 48 (15.5 percent) believed that they had had one previous episode. Eleven (3.6 percent) indicated that they had experienced two previous bouts and three (1.0 percent) stated that they had had three previous attacks. In contrast, only 18 of 356 (5.1 percent) of those denying illicit self-injection stated that they had had one previous episode, and none had had more than two such occurrences.

There has been skepticism about non-A non-B agents being responsible for the multiple episodes, almost all of which have been in long-term addicts. It is stated that in persons with hemophilia and other diseases requiring large numbers of transfusions, this phenomenon has not been seen despite exposure to many hundreds of donors. The frequency of potential exposures to others with acute and chronic infections by hepatitis agents, however, is by no means comparable in chronically transfused patients. The addict has one or more potential exposures every day, depending upon the extent to which he shares or lends his injection equipment. *Every* such exposure of an addict is to one or more other addicts, which is not true of multiply transfused patients.

Treatment

TELFER B. REYNOLDS, MD*

There is no dramatically effective treatment for CAH type B. Interferon therapy shows some promise and is currently being evaluated at Stanford University.[25] Interferon is extremely expensive, has some unpleasant side effects and, though one patient lost HB_sAg during prolonged treatment, most patients have shown only temporary benefit.

In line with the concept that chronic hepatitis B may develop because of poor immunologic response,[26] transfer factor has been used in several centers. In 1974 the patient discussed today received transfer factor prepared by Drs. Harry Cohen and Robert Nystrom from a patient who had recently recovered from acute hepatitis B. He was given five injections at weekly intervals but there was no discernible effect on serum transaminases, HB_sAg titer or clinical course. This was also our experience with a similar patient given larger amounts of transfer factor and studied in considerable detail.[27]

The status of corticosteroid therapy for CAH type B is uncertain, in our opinion. Many physicians assume steroid treatment is indicated because of its proven beneficial effect in two pros-

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pective, randomized clinical trials in chronic active hepatitis patients in London[28] and Rochester.[29] However, neither of these trials included many patients with hepatitis B; when the 17 patients with CAH-B in the Mayo Clinic trial were analyzed separately the effectiveness of prednisone was uncertain.[30] The natural history of CAH-B is still not well described and may differ in some respects from that of the more common type of chronic active hepatitis that is seen predominantly in women, many with extrahepatic manifestations and positive immunologic serum tests. In CAH-B there is a prevalence of males, the overall course usually is longer and often there are prolonged periods of inactivity of the disease with normal or nearly normal serum transaminase levels. Figure 11 shows a life-table survival analysis of 26 patients with CAH-B whom we recruited in 1971 and 1972 for a prospective controlled trial of steroid therapy. For comparison the survival is plotted of the 27 patients with chronic active hepatitis (most non-B) who served as controls in the Royal Free Hospital randomized trial of prednisone.[28] In our group of patients there were some early deaths among those who had advanced disease at the time of random selection. Those without evidence of advanced disease have shown little evidence of progression in the past five to six years. Our trial of steroid therapy was abandoned in 1974 because it seemed

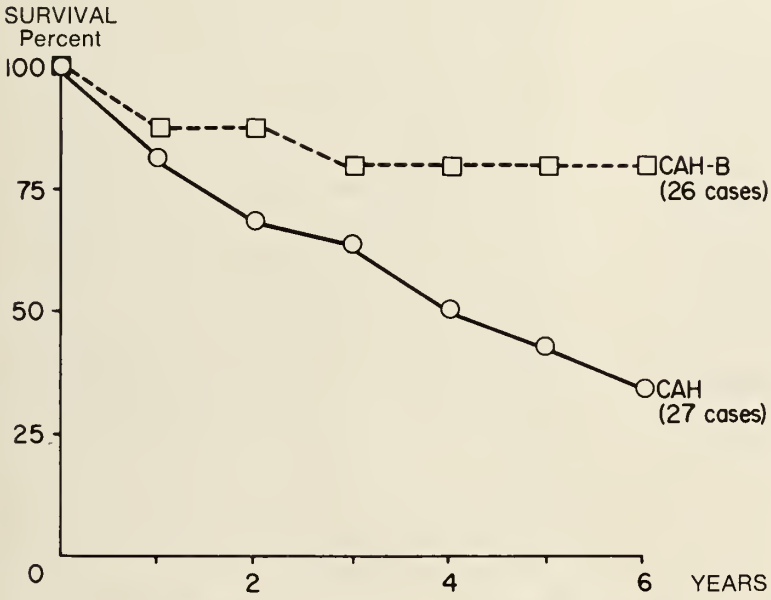

Figure 11.—Comparative survival (life-table method) of 26 patients with chronic active hepatitis type B (USC Liver Unit) and 27 patients with chronic active hepatitis (most non-B) who served as control subjects in a randomized trial of prednisone therapy in London.[28]

TABLE 6.—*Sequential laboratory test results during two exacerbations of chronic active hepatitis B in a male patient born in 1925. Prednisolone therapy was given during the 1963 episode and was not given in 1967.*

	Serum					
Date	*Bilirubin (mg/dl)*	*SGOT (R-FU) (normal, 0 to 40)*	*SGPT (R-FU) (normal, 0 to 40)*	*Albumin (grams/dl)*	*Globulin (grams/dl)*	*Treatment*
2/26/63	6.1	1,000	780	3.0	5.2	
3/25/63	2.5	365	230	3.1	4.4	PRED 30 mg/dl
4/2/63	1.5	55	80	..	..	↓
4/15/63	..	156	..	3.8	3.8	PRED 20 mg/dl
5/27/63	..	365	..	3.6	4.7	PRED stopped
7/1/63	..	194	..	3.6	4.5	
6/12/67	4.2	1,100	1,080	2.6	5.0	None
6/26/67	2.7	336	405	2.2	6.0	↓
7/17/67	1.6	113	89	2.5	5.6	↓
8/7/67	0.7	64	49	2.6	4.8	↓
9/25/67	..	60	33	3.4	4.0	↓

PRED = prednisolone
R-FU = Reitman-Frankel units
SGOT = serum glutamic oxaloacetic transaminase
SGPT = serum glutamic pyruvic transaminase

inappropriate to treat relatively asymptomatic patients with prednisone over a prolonged period in the absence of more obvious evidence of benefit from the medication.

In CAH-B there are often widely separated episodes of activity of the disease that tend to subside spontaneously, making evaluation of any treatment agent difficult. Table 6 shows test results during two exacerbations of CAH-B in a male patient born in 1925. During the first episode of activity in 1963 he was given prednisolone with what we interpreted as a good response. Soon thereafter, a peptic ulcer developed and prednisolone therapy was stopped. Though we followed him regularly we did not detect another exacerbation of the disease until 1967. No therapy was given on this occasion; the rate of improvement in test results was comparable without prednisolone.

Our uncertainty about the benefit from steroid therapy stems from experience with a number of patients in whom we failed to see the expected improvement in biochemical test results when prednisone was given. Table 7 illustrates results in one such patient. Serum transaminase values rose steadily while the dose of prednisone was progressively increased and then fell gradually in a manner that suggests a spontaneous remission more than it does an effect of prednisone.

It is important to find out whether there is benefit from corticosteroid therapy in CAH-B and, if there is benefit, whether it outweighs the risk of chronic therapy. A corollary question is whether treatment should be given continuously over a long period or only during exacerbations of active disease. Currently, we are engaged in another randomized trial, this time of short-term corticosteroid therapy. Patients with CAH-B whose disease is active, as indicated by serum SGOT or SGPT over 160 Reitman-Frankel units, are randomly assigned to eight weeks of therapy with prednisone or placebo with doses beginning at 60 mg and tapering to 20 mg per day. After eight weeks the patients are given the alternative treatment if and when they qualify by having a transaminase level greater than 160 units. Results of this trial in the patient discussed today are shown in Table 8. Neither prednisone nor placebo seemed to be effective. Probably it will be several years

TABLE 7.—*Sequential SGPT values (Reitman-Frankel units, normal up to 40) in an outpatient with chronic active hepatitis B. Prednisone was given from 12/15/73 to 4/18/74 with dosage changes on the dates indicated.*

Date	*SGPT (R-FU)*	*Prednisone dose (mg/day)*
12/15/73	160	10
1/16/74	280	15
1/30/74	755	40
2/7/74	450	..
2/13/74	700	60
2/20/74	600	..
2/27/74	680	..
3/7/74	300	35
3/21/74	502	25
4/4/74	412	15
4/11/74	135	5
4/18/74	..	0
5/27/74	154	..
6/6/74	60	..

R-FU = Reitman-Frankel units
SGPT = serum glutamic pyruvic transaminase

TABLE 8.—*Sequential laboratory test results in patient during treatment with two medications, A and B (one of which was prednisone and the other a placebo). Treatment schedule was 60 mg per day for two weeks, 40 mg per day for two weeks, 20 mg per day for two weeks, 10 mg per day for one week and 5 mg per day for one week.*

	Serum					
Date	*Bilirubin (mg/dl)*	*SGOT (R-FU) (normal, 0 to 40)*	*SGPT (R-FU) (normal, 0 to 40)*	*Albumin (grams/dl)*	*Globulin (grams/dl)*	*Medication*
1/20/77	5.9	179	53	2.7	4.9	A
2/3/77	4.5	83	60	3.2	4.2	A
2/17/77	3.8	108	67	2.7	4.5	A
3/3/77	5.0	236	59	3.1	4.5	A
3/11/77	4.9	160	81	2.7	5.6	stop A start B
3/24/77	5.3	159	64	2.4	6.0	B
3/31/77	6.3	159	58	2.4	6.4	B
4/14/77	5.0	143	53	2.8	6.0	B
4/28/77	5.1	153	37	2.6	5.3	B
5/12/77	4.7	119	36	2.8	5.5	stop B

R-FU = Reitman-Frankel units
SGOT = serum glutamic oxaloacetic transaminase
SGPT = serum glutamic pyruvic transaminase

before the proper place, if any, of corticosteroid therapy in treatment of CAH-B is known. Until more information is available, we caution against prolonged corticosteroid therapy in patients whose disease is quiescent or in those who show neither symptomatic improvement nor a decided fall in serum transaminase levels when therapy is started.

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Refer to: California's Natural Death Act—Medical Staff Conference, University of California, San Francisco. West J Med 128:318-330, Apr 1978

California's Natural Death Act

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. This month's Conference is taken from a transcription of a Medical Grand Rounds sponsored by the Dean's Forum Committee and held January 19, 1977. The discussions are followed by the results of a survey conducted among physicians. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *A group of concerned faculty members from this campus under the heading of the Dean's Forum Committee sponsors this Grand Rounds. The purpose of the committee is "to examine the issues which influence the proper clinical management of patients, particularly those issues wherein physicians' perceptions of the nature of the illness have an effect, where the state of knowledge is such that the management is in experimental phase, where interdisciplinary modes of management may either support, or interfere with, appropriate outcome; and, where ethical considerations and the participation of the patient, in the decision concerning his or her management, are unclear and need definition."*

It has been the privilege of the Department of Medicine to turn over Medical Grand Rounds to the Dean's Forum on two previous occasions. We do so again this morning. I would now like to introduce Dean Julius R. Krevans who will introduce this forum.

DR. KREVANS:† Thank you, Dr. Smith. Our society extends to physicians an awesome privilege, and awesome authority, in the relationships of physicians to the problems which patients bring to them. With that privilege, and authority, goes a very substantial and important responsibility.

In turn, institutions such as ours, which are given the unique charge for education of physicians, have to examine how we structure our education to illustrate that responsibility and privilege are given to physicians dealing with patients' problems. I do not need to defend the rationale whereby we insist that physicians understand the complex interrelationships between the basic sciences and the clinical sciences. Helping a patient is more than understanding science and, in the art of medicine, we have the responsibility to examine these other issues.

We talk about the need for humanity in medicine. Several years ago we had a long seminar on "Humanity in Medicine" on this campus. I attended the seminar and listened to the discussion by a group of sociologists, economists, anthropologists and a variety of other "ists" who had in common only one thing: none of them had ever touched a patient. I became concerned that they were missing a very important point. Toward the end of the conference, the chairman called on me and asked if I had learned anything. I said I had indeed and, as a matter of fact, learned so much that I had evolved instantly a new theory on humanity in medicine which I entitled "The James Barrie Theory of Humanity in Medicine." It goes like this: humanity in medicine is controlled by a group of angels, and every time someone says "provider," instead of physician or nurse, one of those angels dies; and every

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time someone says "consumer," instead of patient or person, another angel dies; and, when all the angels are dead, there will be no humanity left in medicine.

The forum we are having this morning deals with one of these difficult issues. I have asked Dr. Harrison Sadler to conduct the program.

DR. SADLER:* *Thank you, Dr. Krevans. I shall introduce the members of the panel as we go along in order to match the name with the person. The author of the Natural Death Act legislation, Mr. Barry Keene, is here and I am sure before you leave today you can have your questions answered.*

You will see this is a limited bill, applicable only to terminal illnesses and the use of life-support systems. In essence, it is a piece of legislation that encourages a patient to participate in his or her own terminal care and gives legal sanction to his, or her, directive to the attending physician to carry that out.

You physicians will experience a general restlessness: is this not an intrusion on medical care; will it not generate more problems? Perhaps the legislation was necessary as a consequence of increasing feelings of clinical helplessness as physicians experienced coercion, on the one hand, by the presence of scientific and medical technology which was able to sustain life; and, on the other hand, by the fear of suit for malpractice.

I feel, beneath all this, that there is a strange morality which is becoming increasingly popular. It is the assumption that is characterized by the words "why not," and the phrase "if we have it, let's use it." The assumption can be heard daily from patients, from the clinical team, from hospital administrators and, indeed, even from insurance carriers. This bill, then, underscores the role of technology as another clinical option, not a necessity. Primarily it encourages negotiation between physicians and patients over its use. Personally I feel "negotiation" is the key word in what we are discussing today. I am sure we shall have a chance to debate that as the year goes along because we are discovering in another research project called the quality of life in chronic illnesses that this word—negotiation—is the key one in the definition of the quality of life for it involves on the one hand, full information and on the other hand, increasing freedom. This bill is one that tends to enhance the dignity of all, and I think you will see this as the forum goes along today.

One message needs to be underscored for the attending physicians and the house staff: the information to the patient and the negotiations about his, or her, participation need to be considered before *one enters what I call the clinical cul-de-sac. To initiate the use of life-support systems before negotiation with the patient takes us into a clinical cul-de-sac with few options to help us out again. With this in mind, I call your attention to Figure 1, which gives guidelines about the Natural Death Act for patients.*

First, I will call on Dr. Benson Roe. Dr. Roe is a Professor of Surgery whose specialty is cardiovascular procedures.

DR. ROE:† Thank you, Dr. Sadler. The subject of our forum this morning is a direct product of the tremendous advances in medical technology that have taken place over the past several years. It seems that the immense benefits derived from our expanded capabilities are accompanied by some serious problems.

My familiarity with this subject derives from my involvement in the pioneering days of open-heart surgery which were fraught with tragedies and disappointments, as we learned to understand and master the complexities of this particular specialty. Much of modern technology evolved from such experience and, perhaps, that is why I am here today. We learned, at least, to be persistent and not to give up hope.

We once saw patients who did not wake up after a successful intracardiac repair, presumably because of air embolus, and who would remain in coma on respiratory support for very long periods. Often we thought these were terminal cases, yet some of the patients would recover.

How long can we hold on to some hope for recovery? How can we justify continuing the anguish, and the false hope, for the family? How much of our resources, and manpower, can be appropriately diverted to this demoralizing exercise in futility, particularly when it is inevitably at the expense of our other patients? These questions have no undisputed answers and, yet, there clearly comes a time when a situation is futile and further efforts are unjustified. Until now we have had no way of dealing with the problem.

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CALIFORNIA NATURAL DEATH ACT

Guidelines and Directive

These guidelines have been drafted by an ad hoc committee convened at the request of Assemblyman Barry Keene, composed of the Los Angeles County Bar Association's Committee on Bioethics, California Hospital Association Legal Counsel, California Medical Association Legal Counsel and representatives of the Office of Assemblyman Keene.

GUIDELINES FOR SIGNERS

The DIRECTIVE allows you to instruct your doctor not to use artificial methods to extend the natural process of dying.

Before signing the DIRECTIVE, you may ask advice from anyone you wish, but you do not have to see a lawyer or have the DIRECTIVE certified by a notary public.

If you sign the DIRECTIVE, talk it over with your doctor and ask that it be made part of your medical record.

The DIRECTIVE must be WITNESSED by two adults who (1) are not related to you by blood or marriage, (2) are not mentioned in your will, and (3) would have no claim on your estate.

The DIRECTIVE may NOT be witnessed by your doctor or by anyone working for your doctor. If you are in a HOSPITAL at the time you sign the DIRECTIVE, none of its employees may be a witness. If you are in a SKILLED NURSING FACILITY, one of your two witnesses MUST be a "patient advocate" or "ombudsman" designated by the State Department of Aging.

You may sign a DIRECTIVE TO PHYSICIANS if you are at least 18 years old and of sound mind, acting of your own free will in the presence of two qualified witnesses.

No one may force you to sign the DIRECTIVE. No one may deny you insurance or health care services because you have chosen **not** to sign it. If you **do** sign the DIRECTIVE, it will not affect your insurance or any other rights you may have to accept or reject medical treatment.

Your doctor is bound by the DIRECTIVE only (1) if he/she is satisfied that your DIRECTIVE is valid, (2) if another doctor has certified your condition as terminal, and (3) at least 14 days have gone by since you were informed of your condition.

If you sign a DIRECTIVE while in good health, your doctor may respect your wishes but is not bound by the DIRECTIVE.

The DIRECTIVE is valid for a period of five years, at which time you may sign a new one.

The DIRECTIVE is not valid during pregnancy.

You may revoke the DIRECTIVE at any time, even in the final stages of a terminal illness, by (1) destroying it, (2) signing and dating a written statement, or (3) by informing your doctor. No matter how you revoke the DIRECTIVE, be sure your doctor is told of your decision.

Figure 1.—Guidelines developed for signers of California's Natural Death Act.

I believe, however, that the time has come for us to acknowledge and define our limitations. When our obligation to do everything possible for an individual patient is in conflict with our overall responsibilites, then we are in trouble and we need help.

The Natural Death Act is a very important step in that direction and, most significantly, it acknowledges public and legal involvement in a problem which, until now, the physician has had to shoulder alone and which many times has made him behave senselessly, inhumanely or, surreptitiously, illegally. I think it is not unreasonable to suppose, or to assume, that further advances of expensive medical technology will soon reach the stage where even our affluent society will no longer be able to underwrite a blank check for health care if every hospital death is to be accompanied by a $100,000 effort to sustain life. The Keene Bill is a landmark beginning—a start at finding solutions for complex, knotty future questions concerning the physician's role in the dying process.

DR. SADLER: *Mr. Barry Keene represents the north coast counties in the California Assembly. He is a lawyer by profession and the author of this legislation. Thank you very much for coming, Mr. Keene.*

MR. KEENE:* Let me begin by issuing a disclaimer concerning my role here today. I appear before you not as an expert but more as an historian. I have no true expertise in medicine, although I learn more about health care daily, and I am certainly responsible for policy decisions in that field at the legislative level. I am not an expert on death and dying, although I have had occasion to resort to much of the literature. I am certainly not, nor would I ever presume to be, an expert on ethical questions, having learned what I have about human nature in the course of the legislative process and all of its complexities. What I am able to do is relate to you the personal considerations and the group dynamics that led to the passage of the Natural Death Act.

The bill is not well-founded in empirical data. It is largely the product of some personal experiences, not only mine but also those of people in the medical field, in the ministry and in the legislature—all of whom have had some intimate acquaintance with the process of dying. We did interview physicians; we did contact tertiary care centers; we did talk to nurses. We did gain insights from them. We did also speak with some terminally ill people and we gained insights from them as well.

Is there a need for the bill? Is legislative intrusion, or intervention, justified in an area such as this? One of the things we determined is that the question produces a great deal of anxiety in the course of the relationship among physicians, hospitals, nurses, clergy and relatives and the terminally ill patient. It produces anxiety for all of them, even the people who say everything is all right but who do not want to talk about it; those who do not want to tell you what happens, but who assure you everything is being taken care of. The doctors, in many instances, are placed in the position of making a decision which is not only a medical judgment, for which they are trained, but also an ethical judgment. That produces anxiety.

Physicians, we are told, will have a better feeling for and insight into this attitude. Physicians are trained to keep people alive. Perhaps this spills over into situations even when they are not able to do so. As for a terminally ill patient, he or she often feels in a kind of custodial situation —that is, under the control of forces which are beyond one's own right to self-determination. This consideration is an important feature of the bill.

As you doctors well know, many of my colleagues in the legislature are attorneys and, therefore, are concerned with constitutional rights and with individual liberties. There are a cluster of individual rights which we felt were being denied to terminally ill patients; for example, due process before having one's body placed in a custodial situation where others are making the decisions. One of the most intimate and potentially offensive acts is invasion of the human body itself without that decision having been made, or necessarily assented to, by the terminally ill person. Finally, one must consider the whole question of individual self-determination; why should self-determination be denied to people who are terminally ill?

The opponents of the measure felt it was a foot-in-the-door leading to euthanasia: soon we were going to be "killing" other categories of people—the retarded and the elderly, for example. We had two responses. The first was that this differs from the offensive aspects of euthanasia. It is not someone else deciding when a person ought to die, except with reference to objective

*Honorable Barry Keene, Chairman, Assembly Committee on Health, State of California.

factors. The terminally ill patient, in a prospective way, makes the decision. The second aspect that distinguishes this from euthanasia is that we are not talking about a category of people and determining *whether* they ought to die, but *how* they ought to die. Those most affected by the prospect of dying ought to determine how their final days are to be spent.

The American Medical Association misunderstood the bill. They, and some other opponents of the bill, felt this would be the exclusive mode of determining when a terminally ill patient would have life-support systems removed. That is not the case. This is a parallel procedure. The measure specifically states that it does not affect the law with reference to the removal of life-support systems in situations where directives have not been prepared. The California Medical Association studied it much more carefully; therefore, they took a different position on the measure.

We also had to deal with political problems. We were presented with ideas from the opposition, some of which were good ideas, making it necessary to move more slowly than originally anticipated. We did not want to get into a lot of collateral ethical issues. We could not handle all of those at the same time. We wanted the legislature to concentrate on the key issue—the rights of the terminally ill. We did adopt a two-tier procedure. First, if a person is not terminally ill at the time he or she makes out the declaration, the doctor may (and, based on samples we have taken, probably would) effectuate the directive. The notion was that a person not terminally ill would not be capable of making as sober a judgment on a question like this but, at least, the doctor involved would have a directive providing some orientation about the earlier feelings of the person who becomes terminally ill. They were prevented from doing so by fear of liability and by pressures from relatives who are close by. As for a terminally ill person who wishes to make out a directive, it was felt that at the time of the diagnosis he or she is in no emotional state to prepare a directive of this kind, such that it should be effectuated without question by the physician. So, a 14-day period was allowed to let the patient consider the situation and to determine whether he or she really wanted to go ahead. At that point, we felt that so serious and sober a consideration had been given to the question that the doctor ought to be required to effectuate it. That is provided in the bill.

We provided formalities in the preparation, and signing, of the declaration that are very similar to those of a will. We did not call it a will because that causes legal confusion; wills by definition are effectuated after a person has died. We provided for revocation, an act which does not require the same degree of formality as the preparation of the document. It is quite easy to revoke the document but the revocation must be communicated before anyone is held responsible for knowledge that the directive is in fact revoked. The clause that the directive could not be effectuated if the signator were pregnant was one of the collateral ethical issues we simply did not want to get involved in. It would have brought the whole question of abortion into the legislative dialogue. We did not want beneficiaries, and others who might stand to gain some advantages, to be witnesses to the directive. There was some feeling that people in nursing homes, because they were unaccustomed to making independent decisions by virtue of their situation, ought to be further protected. Therefore, we provided for one of the witnesses in the bill to be a state-authorized ombudsman, or representative, for these people. For people who prepared one of these directives at a time when they were not terminally ill, we felt there ought to be a five-year gap. They would have to sign one of these directives again after five years to make sure the judgment they originally made was one about which they were serious, and that they had not changed their minds.

To sum up, we felt there were people who in the event of terminal illness would not want to spend their final days tyrannized by machines when the only purpose (and this is the key language) of those machines is to postpone the moment of death artificially where no cure is possible and where death is, in any event, imminent. Some of the critics have asked what we mean by imminent. How can we be sure the diagnosis is one of terminal illness? The answer is that we could not pass bills that provide, with a great deal of specificity, what really amounts to a medical judgment. There is a certain amount of subjectivity in every bill we write. We prepare legislative policy and, to some extent, we leave the people affected by that policy in an uncomfortable position of filling out a lot of the details. We probably have made mistakes in some of the provisions of this legislation. There will be better ways of handling certain of the procedures, different ways of handling them which are more conducive to

our purposes. These better approaches will be a product of the kind of discussion you are having here today. The bill essentially substitutes, in exchange for the ad hoc kind of decision-making which exists today, a prospective decision by the patient in the form of a directive to the physician that meaningless life-support systems be removed if death is imminent and, of course, provides a freedom from liability for the physician who does effectuate one of these directives.

DR. SADLER: *Thank you, Assemblyman Keene. I think you can sense why it is necessary to have someone who is conversant with ethics on every medical campus. May I present Dr. Albert Jonsen, Associate Professor of Bioethics.*

DR. JONSEN:* What are the ethical issues raised by the Natural Death Act? I wish to state what I see as the ethical import of the Act itself; then, I shall venture some predictions about its ethical implications.

The import of the Act itself might be summed up in four propositions:

1. It is a statement of an already well-recognized legal right; namely, the legal right of persons to refuse medical treatment. This has been made clear by American courts during the last half century with certain specific qualifications, such as there being no harmful consequences to others as a result of the refusal. The Act not only makes this statement but also applies it to a situation not made entirely clear by earlier precedents; namely, the legal force of a directive given in anticipation of the event; that is, the critical period when death is imminent and the patient unable to express his or her will. It also seeks to clarify another cloudy area: the matter of the criminal or civil liability of those who honor such a directive although, despite the theoretical possibility of indictment and conviction, only a handful of cases has been reported and few have ever come to trial. No conviction has ever been handed down and, as Curran and Shapiro write in their *Law, Medicine and Forensic Science,* "There is no American appellate court decision involving euthanasia and a physician." Still, this specter is banished (for at least one sort of case) and reasonable personal and clinical decisions are no longer menaced.

2. The Act is an acknowledgment of the moral autonomy of persons to control their own lives at a time when their actual ability to exercise such autonomy is most compromised. As such, it is a manifestation of the moral principle of respect. While the question of suicide and its abetment may be raised, I do not think that in general any reasonable case can be made that the moral definition of suicide is applicable when medical treatment, which is essentially incapable of restoring function, is refused. This legislation makes it clear that legally such an act cannot be defined as suicide.

3. The Act is a reaffirmation of the long tradition in medical care that the determination of the inefficacy of treatment lies in the hands of the physician and the determination of the undesirability of treatment lies with the patient. Sensitive physicians have always known decisions about dying, difficult as they may be, are in some very important sense mutual and reciprocal decisions. This act confirms such awareness.

4. The Act is a warning that the high degree of organization and efficiency demanded by current technology should not be allowed to overwhelm the humanity and the needs of the dying patient. It inserts into the technological setting an imperative to respect the most humane and tragic of decisions, the decision to no longer live.

I shall venture several predictions about the implications of the Act:

1. Little will change in the actual course of clinical practice. Physicians must still diagnose terminal illness and determine terminal condition, with all the uncertainty, anguish and occasional error involved in those acts. The evaluation of patients will require time, repeated interventions, tentative efforts before the definitive judgment. Even that judgment will be definitive more because of instinct and experience than evidence.

2. The Act will not open the floodgates to a cascade of euthanasia or to an orgy of mercy killing. On the other hand, one adverse side effect may be to make physicians, who do not understand the Act or its intent, even more reluctant to follow good clinical judgment and discontinue treatment for those who do not present the requisite directive. This would be a most unfortunate misunderstanding.

3. The Act will relieve much of the moral anxiety, if not the psychological anxiety, when the directive is mandatory in the case of the "qualified patient" and when family, or other interested parties, are in distressed perplexity or urge the physician to continue treatment which

*Albert R. Jonsen, PhD, Associate Professor of Bioethics, University of California, San Francisco.

in his, or her, judgment is of no avail. In such a case good clinical judgment, fortified by the patient's directive, overrides the opinions of others which may be distorted by grief, guilt and sometimes greed.

4. The Act will initiate pressure for more precise, detailed and recorded orders regarding resuscitation of terminally ill patients. This pressure, which has been resisted by many physicians and even by legal advisors, will lead to establishment of categories of patients in intensive care, as has already been done at the Massachusets General Hospital and the Beth Israel Hospital in Boston. The problems attendant on such classifications will have to be faced with care and honesty.

A variety of particular questions of interpretation will arise in the course of practice. Is a patient in renal failure "in a terminal condition" since dialysis can reverse the condition? Is the administration of insulin one of those "life-sustaining procedures" which can be withheld? Is administration of blood to an exsanguinating patient "a mechanical or artificial means"? How is a patient, after there has been a diagnosis of terminal disease—say, glioblastoma—and after having signed a directive, to be treated when brought to the emergency room moribund from barbituate poisoning? Such questions will have to be answered by careful study of the legislative language, by accurate presentation of the circumstances and by common sense. Their interpretation hinges, I believe, on the very important words of the Act, "artificially prolong the moment of *death* . . . where, in the judgment of the attending physician, death is imminent *whether or not* such procedures are utilized."

A final comment. Every effort to modify major social patterns, whether by law, by invention or by ideas, can be seen either in its broad sweep or in its fine details. If the broad sweep is missed and only the fine details picked out, the effort is distorted. If only the broad sweep is noted and the fine details neglected, the effort is empty. It is the duty of the profession to understand the intent of this legislation, recognize the real and imagined problems which inspired it and to come to grips with the many questions of detail, in expression and application, which it represents, thinking them through as they apply to real clinical situations and expressing them in clear and sensitive policy.

DR. SADLER: *Let me invite you to meet a patient whose case illustrates the clinical features of the Natural Death Act. Dr. John Solters, who is a Fellow in Nephrology, will present the overview.*

DR. SOLTERS:* Mr. J is a 49-year-old man in whom end-stage renal disease is secondary to diabetic glomerulosclerosis. Diabetic complications include lower extremity neuropathy but no significant ocular or cardiovascular problems. Mr. J began maintenance hemodialysis at the University of California Renal Center in November 1973. He has had a multitude of vascular access procedures with significant attendant morbidity. A summary of these events is as follows.

The patient began dialysis with a left thigh saphenous vein graft which clotted irreversibly after 4½ months. A silastic cannula was then inserted in his left forearm and functioned well for 14 months until March 1975. At this time a bovine graft was placed in his right forearm. This graft clotted but thrombectomies were done on eight separate occasions and lasted a total of 12 months. Another silastic cannula placed at his left ankle functioned for a few weeks so that, in April 1976, a bovine graft was placed creating a fistula in the patient's right upper arm. This access lasted two months and clotted secondary to infection.

In June 1976 a bovine graft was then placed in the left upper thigh and functioned for only five weeks. An abscess had developed around the graft and a resultant pseudoaneurysm required emergency arteriotomy and graft ligation. Unfortunately, the graft was not removed entirely and draining sinuses persisted for several weeks.

Since February 1976 dialysis has been carried out in the patient reliably via a silastic cannula in his left forearm. He has undergone a revision of the venous limb in April, an arterial revision in June and a second venous revision in August 1976. This access has very low blood flows, but fortunately no high venous resistance when the blood pump is used. The shunt has clotted several times but has been successfully declotted each time. The patient's family administers heparin via a T-piece at home, and the patient is receiving aspirin by mouth.

For the past six months, Mr. J has noted severe functional impairment of his right hand and left foot. He has a foot drop with pronounced wasting, weakness and unobtainable nerve conduction velocities in the leg. Ulnar and median nerve

*John Solters, MD, Fellow in Nephrology, Division of Nephrology, University of California, San Francisco.

damage is documented in his right hand. The patient writes with great difficulty and cannot hold objects for a prolonged period. His gait is hampered by the foot drop; he required crutches and can no longer drive his car. Efforts at physical rehabilitation have not altered his disability.

In November 1976 Mr. J met with Dr. Robert Lim, his surgeon, and discussed the possibilities of further access procedures. Dr. Lim proposed access placement sites in the left upper arm as well as Thomas shunt placement in a thigh. The patient declined any further procedures when he learned that functional impairment of the operated limb was a continued risk. Peritoneal dialysis via a permanent peritoneal catheter at home was offered and declined. The patient's age and diabetes have prevented serious consideration of transplantation.

The patient is well aware that when dialysis can no longer be carried out via his cannula, his death is imminent. In that event, he has left written instructions that no surgical or mechanical means be employed to prolong his life.

Mr. J is married and has four children. His wife sympathizes with his position but feels he should agree to further surgical procedures. Deprived of his customary social outlets, the patient spends his time at home watching television or napping. A recent bout of hepatitis with consequent food and stool precautions has decreased social contacts at home. He currently anticipates thrice weekly dialysis as an opportunity to socialize. Appetite and energy levels had responded to administration of amitriptyline hydrochloride (Elavil®), which was discontinued when the patient reported possible hallucinations.

DR. SADLER: *Mr. J, how does it feel to have all these things going on about you? You realize you are a pioneer because you really signed this bill before Mr. Keene got it through the legislature.*

MR. J: Well, I told the doctor I did not want any more operations because of the way I feel. The doctor actually asked "Do you know what you are saying?" I said "Yes, I do." He said "When this graft in your arm goes out, that's it, because that means death." I asked "What does that mean? Go through another operation, taking a chance that nothing may happen?" I said "I prefer not to have another operation. This may last for ten years and it may last for ten weeks; I do not know. Whatever time it lasts, I'll be satisfied with that—but, no more operations."

DR. SOLTERS: *Mr. J, you first brought this up to me about six months ago, is that right?*

MR. J: About six months.

DR. SOLTERS: *We talked about it then. I assured Mr. J at the time that his body was his own and he could say what was to be done with it. If he did not want any further accesses, it was his decision so long as he was well aware of what the consequences would be.*

Mr. J, it perked along in your head for some time before you actually made the decision. We talked about it in the summertime, and you signed the directive in November.

Ms. Kathleen Lavery is our nurse. Ms. Lavery, can you tell us about some of the conversations you had with Mr. J about this?

MS. LAVERY:* Mr. J expressed to me, after the last surgical complications, that he did not want any more procedures done. I asked him, was he sure? Had he made up his mind this was what he really wanted? I respected him for making the decision, and I relayed this information to the doctor to make sure he understood how Mr. J felt. Then we took it from there, having several meetings with the medical staff and the medical team to make sure Mr. J was aware of the consequences.

DR. SADLER: *As a nurse, did you feel much anguish about this whole procedure?*

MS. LAVERY: Yes, there was much anxiety on my part and on the part of some other staff members. Also, there was frustration and helplessness, not knowing what else to do. In a way I also respected Mr. J's decision to do this because there were really no more alternatives for him, and he would just suffer more.

DR. SADLER: *Ms. Elaine Fripp is the social worker on Mr. J's case. Ms. Fripp, do you have some feelings about it?*

MS. FRIPP:† The extent of social-work intervention in a case such as this largely depends on the institutional setting and the internal climate of that setting. Take, for example, dialysis as a form of treatment. It is not given in isolation. You

*Kathleen R. Lavery, BSN, RN, Senior Staff Nurse, Renal Center, San Francisco General Hospital.

†Elaine Fripp, MPH, Clinical Social Worker, Dialysis Unit, San Francisco General Hospital.

have to think about the effects of this decision on the other patients, the family and the staff; and, as a social worker in this setting, I see my role mainly as maintaining, establishing or reestablishing communication in the patient's network of human relationships. In addition I have been studying the status of "social death," in which patients give up social contact and withdraw into a deep personal enclave. When this happens they are hard to help and often develop increasing medical complications.

DR. SADLER: *I would like to introduce Dr. Hillary Don, director of the Intensive Care Unit, Moffitt Hospital.*

DR. DON:* I am impressed with this patient's personal courage and dignity. I want to turn to a slightly different aspect of the Natural Death Act, that is, its relationship to the Intensive Care Unit and its effects within this hospital.

The Natural Death Act addresses the issue where the indignities and misery sometimes inflicted on patients provide nothing medically necessary or beneficial to that patient. It has always been the patient's right to refuse treatment. It has never been labeled suicide for a patient to refuse treatment and such a decision has been invariably respected by physicians and by the law. This will not be altered by the Natural Death Act.

However, the second category, in which a patient who may or may not have signed a declaration is comatose or cannot make a decision, is one which I want to talk about.

If a patient has signed a declaration before this episode, the physician is bound to use his judgment as to whether to fulfill the directive. This has always been a physician's duty and his responsibility: to make a judgment about what he believes his patient would, or would not, like. The central figure is the patient. It is not I, the physician, who may be frustrated by the complexity and the persistence of the patient's problem and who may wish to resign from it. It is not the state, which might be anxious about the cost of medical care. It is not the relatives who may be overburdened by the constant awareness of a relative who might die. You can see the amount of bias any one of these parties will introduce. In this situation, then, the physician makes a decision that death is inevitable and imminent and, following discussion with the relatives, all support is withdrawn. The Natural Death Act does not alter this relationship between you and the patient. This conduct has always been that which we would expect.

The problems associated with the care, and the handling, of the dying patient unfortunately, I believe, go far beyond the confines of the Natural Death Act.

Is death inevitable? The definition and decision about inevitability of death is one which will come to different people at different times in the care of the patient, and the attitude I have is that there will come a time when it will become obvious to all the staff that death is inevitable. The bill states "if death is imminent, with or without supportive care." The problem with that is: What if death is not imminent with supportive care? It seems to me the problem is when life can be maintained, and death is not imminent in the face of your supportive care. It is an issue which is outside the confines of the present Act. Finally, presumably the Act is not to protect us, the physicians, against litigation. Such protection cannot be a motive for the Act, or we will be unprotected if the patient had not signed the directive.

In conclusion I would say that the Act will not end debate and doubt. It may in fact produce more doubt; it may in fact introduce interpretation, and misinterpretation, by lawyers and laymen, of each word and phrase. However, in the face of this, the great advantage of the Act is that it has opened this dialogue and from such dialogue it is to be hoped that satisfaction for patients, the relatives and the physician will be achieved.

DR. SADLER: *Thank you, Dr. Don. The audience may now direct its questions to the panel.*

QUESTION: *What is the responsibility of the hospital, or the physician, to bring the Act to the attention of a patient?*

ANSWER (Assemblyman Keene): I would suggest to you that there is probably an ethical duty and not a legal duty. The exact definition of that duty is one which would best be determined by a group, such as this, in their own discussion.

QUESTION: *Specifically with regard to the patient presented today, I do not understand the relevance of the Act. First, is this patient considered imminently dying? Second, is his expiration binding on the physician? Further, since the patient is*

*Hillary F. Don, MD, Associate Professor of Anesthesia, and Director, Intensive Care Unit, University of California, San Francisco.

required to sign a consent-for-surgery form to begin with, isn't the directive redundant in this situation, and is it in any way binding on anyone?

ANSWER (Dr. Sadler):—Would you accept that, when he re-enters the hospital for the revision of his shunt, and does not want it, and dialysis then is discontinued, death would be imminent and that dialysis does replace a vital function? What is binding is his directive for no more surgical procedures or life-support efforts.

QUESTIONER: *I think the signing of the directive, and the timing of that signing, would do nothing but confuse me. If I were in the emergency room when the patient came in, I would not know whether his doctors considered he was imminently dying. If he were imminently dying and since he signed the directive 14 days after the diagnosis (or more than that), would I be bound not to offer him surgical treatment under those circumstances? If it was clear he were imminently dying at the time of the decision, the legal ramifications of that are totally different than if he were not.*

ANSWER (Assemblyman Keene): I think you are confusing two states: that of the diagnosis of terminal illness and that of the imminence of death. With reference to the first, if the directive was signed at a time when the person was authorized as a qualified patient who is terminally ill by diagnoses of two physicians, the doctor is required to effectuate the document; but, the actual effectuation does not occur until death is imminent whether or not the life-support systems are utilized.

QUESTIONER: *I still do not understand whether he is legally, at the present time, imminently dying.*

ANSWER (Assemblyman Keene): Well, death may not yet be imminent but, as I understand it, it will be imminent somewhere down the line and, at that point, life-support systems are to be removed because the terminally ill patient will have decided he does not want them used if they serve no purpose except to postpone the moment of death.

QUESTIONER: *Which is the life-supporting system, the kidney machine or the access?*

ANSWER (Dr. Sadler): It would seem to me the shunt is part of the life-supporting system. It is simply a necessary artificial extension.

DR. SOLTER: I would just like to make one brief point. Mr. J's death is imminent when he no longer has vascular access and that is when the instructions are operative.

DR. SADLER: *Mr. J, do you understand what all this is about? They really wonder why you signed the Act.*

MR. J: Well, I am just going to tell you this. I have had 19 operations and I do not want to be cut open any more.

DR. SADLER: *The question would be, when that time came, why not just stay home and let nature take its course?*

MR. J: Makes no difference to me, whichever way they want it.

DR. SADLER: *However, if you are brought into the hospital, you want them to understand how you feel and carry out your wishes?*

MR. J: Right.

DR. SADLER: *Thank you.**

DR. LACKNER† (From the audience): It is known that I recommended to the Governor that this bill be vetoed. Let me explain my difference of opinion. I personally feel the legislation, although well-motivated, is ill-advised. I say this personally because Governor Brown disagrees with me about this. He feels that this is very good legislation. I also feel that there are certain things which are good about the legislation: first of all, it is good to establish that refusing treatment is not suicide, and that refusing treatment should not make it possible for insurance companies to decline to meet their commitments. I feel it is good to allow people to look toward some possible future state of incompetency and to make a determination which will help guide their therapy during that state of incompetency. Beyond these points, I have some very serious concerns.

I believe that all patients at all times, if they are competent and not under duress, have the right to decline all therapy. This goes for terminal patients and nonterminal patients. It goes for

*On February 1, Mr. J returned to the hospital for his dialysis with his shunt already clotted. Attempts to declot it were unsuccessful. He allayed the anxieties of the staff and reassured them that he fully understood the consequences of this medical problem and his directive that nothing further be done. He returned to his home but was readmitted in three days at the request of his family. Again he was dignified and stoical, again reassuring the staff not to worry, they had done all they could do. Three days later he died. Each member of the staff was deeply moved by his continuing dignity.

†Jerome Lackner, MD, Director, California State Department of Health, 1975-1978.

terminal patients whose death is imminent and terminal patients whose death is not imminent. It goes for terminal patients who have artificial, and mechanical, means of life support and it goes for those who have nonartificial and nonmechanical means of life support. Furthermore, I feel it is wrong to separate out dying patients from nondying patients. I think the emphasis should be on the right of all patients, at all times, to make decisions about their own care; that is, for them to be the primary decision-makers.

I do not believe someone should have to be a qualified patient before the Act applies. I do not believe you should make a distinction between those who have been certified within 14 days, and those who have not. Furthermore, I think it is wrong to make one single kind of form by which a patient can express this will. We can dispose of our property in many different ways and, yet, we can take care of this very important act in only one way.

My major fear about this bill is that if our colleagues are given one narrow exculpatory route from liability, then all of those people who do not fit into that narrow pattern will have a harder time to die. Most of us have not made wills regarding our property and most of us will not make wills regarding our termination. I am fearful that those of us who have not made wills regarding our termination will be assumed to have not wanted the physician and the family to make judgments about our termination in the event of our incompetence.

I want to point out, however, that I do not speak as the Director of the Department of Health of California; I speak just as a private, individual clinician. The Governor feels it is a good bill. I certainly respect Barry Keene. He is one of the finest health legislators in the state and perhaps in the nation, but I do strongly differ with him over this bill because I think it constricts severely the right to die. It creates more problems for those of us who are trying to help people when they are dying.

QUESTION: *I wonder if someone could expand a little bit on the provisions of the bill for those terminally ill patients who are considered to be of impaired judgment, perhaps for psychiatric reasons.*

ANSWER (Assemblyman Keene): There are a series of circumstances in which a patient would be incompetent and make certain demands upon the attending physician. I suppose that if the physician had reasons to suspect that the patient was incompetent at the time he prepared the directive, the physician ought not to effectuate the directive. He ought to operate under the law as it is now.

QUESTIONER: *However, it does not state the competency of the patient in the way the competency of a person who makes a will is stated in the will.*

ANSWER (Assemblyman Keene): If the patient becomes incompetent for whatever reason and if the patient was competent at the time he or she prepared the directive, it ought to be effectuated because those are exactly the situations for which the terminally ill patient wishes to prepare. The several situations with which the bill does deal are if the terminally ill patient is comatose; if the patient is incompetent; if the patient is not comaose but perhaps so severely sedated that he or she is considered to be incompetent, or if the patient is rational and the physician will not pay attention to the directive or the wishes of the patient. I have met several physicians who have told me that they will not effectuate these directives. Now, the standards of the profession may be different, the expectations with reference to those physicians may be different, but they will simply not listen to the terminally ill patient. They consider the patient, by virtue of his or her physical condition, to be in a kind of custodial state. That is what the bill deals with and that is what the bill is intended to deal with.

DR. SADLER: *We thank the panel for their comments; and, Mr. J, we are very grateful to you for attending this important meeting.*

Refer to: Klutch M: Survey results after one year's experience with the Natural Death Act—Sep 1, 1976-Aug 31, 1977 (Appendix to Medical Staff Conference—California's Natural Death Act). West J Med 128:329-330, Apr 1978

Appendix

Survey Results After One Year's Experience With the Natural Death Act

September 1, 1976 - August 31, 1977

MURRAY KLUTCH, *San Francisco*

IN SEPTEMBER 1976 California became the first state to enact a law (AB 3060, the Natural Death Act) establishing the right of a person to instruct his physician to withhold or withdraw life-sustaining procedures in the event of a terminal illness or injury. Incorporated into the Act was a section titled "Directive to Physicians" which required the signatures of the declarant and two witnesses. Also included in the Directive and throughout the Act were a number of provisions which were the result of legislative compromises stemming from opposition to the concept of the bill or to specific features in it.

During the course of the year many questions were raised concerning the experiences of physicians with the Natural Death Act. In an effort to secure such information, as well as to determine whether the Act had changed the way in which physicians practice medicine and whether or not it was serving a useful purpose in their practice, a questionnaire soliciting comments and suggestions was mailed to a group of 168 physicians. Each of these 168 physicians had ordered a minimum of 100 copies of the separately published Directive to Physicians, which also contained guidelines for its use by patients and physicians. It was presumed that physicians ordering multiple copies of the Directive would be more likely to provide us with more complete information about their experiences in the use of the form.

In the five weeks following the September 19, 1977, mailing of the questionnaire 112 replies were received, a response rate of 66 percent. Replies came from physicians in some 75 areas of California representing a virtual cross section of urban and rural communities. Doctors engaged in family practice, internal medicine and general practice accounted for 71 percent of the returns, with the remaining 29 percent of the respondents engaged in some 11 other specialties of practice. Of those responding, 61 identified themselves as in solo practice, 20 were members of groups composed of from two to five physicians, and five were members of groups with more than five doctors. Twenty-six provided no information on the size of their practice group. Eighty-six of the 112 respondents reported that they represented a total of 231 physicians. Twenty-six did not answer the question.

The following summary of the replies of the 112 respondents to the questionnaire provide insight into the evaluation of their experiences with the Natural Death Act during the first full year of its operation:

- Just over half of the respondents stated that the Act has been useful to them; the major reason being that it helps improve relationships with the patients and the families of patients, and that it is now easier to withhold or withdraw life-sustaining procedures. Several respondents mentioned that the Act provided a mechanism for patients to communicate with their physicians and also has served to bring the subject "out of the closet" making possible open discussion between patients and their families.
- The remainder, slightly less than 50 percent, stated that the Act served no useful purpose because they practiced medicine no differently than they had before the passage of the Act, or that the Act merely gave legal sanction to their medical decisions. Several also noted that they had difficulty in interpreting some sections of the Act,

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while others reacted to what they considered to be restrictions imposed by the law.

- As might have been anticipated, 93—the overwhelming majority of respondents—have not had occasion to utilize the Directive to Physicians in withholding or withdrawing life-sustaining treatment. A total of 53 physicians, as represented by 19 respondents, made use of the Directive signed by an estimated 67 patients.
- Almost 50 percent of the respondents did not believe that the Natural Death Act required revision; 17 percent were uncertain or questioned whether a revision was needed while 16 percent did not reply to this question. The remaining 17 percent of the respondents believed that some revision would be helpful or necessary. Several respondents thought that the Act's language itself should be clarified. Among other suggestions: eliminate differential between qualified and unqualified patients; do not require witnesses; clarify the role of the ombudsman, and do not require renewal of the Directive after a five-year period. Several of those making the latter suggestion questioned the necessity of executing or reexecuting the Directive within the 14 days specified in the Act. Many of these suggestions had been made at the time AB 3060 was being considered by the legislature. The fact that they have surfaced again after one year's experience indicates the importance of reconsidering them in future revisions of the legislation.

The questionnaire provided space for additional comments. The commentary of 18 respondents served to reinforce responses previously made to the effect that:

- The Natural Death Act has not resulted in a change in the way in which physicians practice medicine.
- The Act has been a positive force in encouraging patients and their families to discuss the subject of terminal illness.

Several physicians raised some questions peripheral to the subject matter of the Natural Death Act. These questions were more directly related to the issue of the prolongation of a person's life where the situation was not a terminal one but where there was little if any hope for the patient to assume more than a vegetative function.

Although the survey results are not based upon the replies of a representative sampling of physicians, the fact that the majority of respondents have not had occasion to utilize the Directive suggests that an insufficient period of time has elapsed to evaluate the effect of this legislation, coupled with the fact that perhaps only a small percentage of the population has as yet signed a Directive.

Important Advances in Clinical Medicine

Epitomes of Progress — Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

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Skinny Needle Percutaneous Transhepatic Cholangiography

IN PROLONGED JAUNDICE, differentiation between mechanical obstruction and intrahepatic cholestasis is sometimes impossible, even after all relevant laboratory tests and liver biopsy studies have been done.

A major problem in the radiologic investigation of jaundice is the inconsistency of biliary tract opacification using presently available intravenous contrast media. Ducts are rarely shown when the serum bilirubin is greater than 4 mg per dl and cholangiography often fails with levels between 2 and 4 mg per dl, especially if the jaundice is prolonged or the serum bilirubin is climbing.

The introduction of percutaneous transhepatic cholangiography (PTC) resulted in a major improvement in radiologic investigation in patients in whom simple methods had failed.

Earlier investigators preferred an anterior approach, but the risk of an intraperitoneal bile leak, caused by inadvertent puncture of the gallbladder or extrahepatic ducts, was always a possibility. There was an added risk of liver laceration by relatively inflexible, large-bore needles (17 to 20 gauge). Because of frequent complications PTC was only done at a time when the early laparotomy could be done. With the introduction of the Chiba technique, using a fine flexible needle 0.7 mm in diameter, several important advantages became evident.

The percentage of successful studies rose significantly in both obstructed and unobstructed systems, the improvement being most pronounced in the latter, and there was a dramatic decrease in the complication rate obviating the need for early laparotomy.

Success rates of 90 percent to 100 percent in obstructed ducts, 25 percent to 67 percent in unobstructed ducts and complication rates of 5

percent to 7.6 percent have been recently recorded.

A lateral approach allows radiologists to continuously inject contrast medium under fluoroscopic control without exposing themselves to excessive radiation, and in this way entry into a bile duct is quickly recognized. If the needle enters a dilated bile duct, decompression is undertaken before opacification is attempted. Multiple spot films are taken in various projections, including standing, followed by overhead supine and prone films. In this way the level of obstruction can be identified and the cholangiographic appearances usually permit a specific diagnosis to be made.

PTC is a valuable technique that provides important anatomic information in cases in which conventional diagnostic examinations of the gallbladder and bile ducts offer no help. It permits differentiation of obstructive from hepatocellular jaundice and provides definitive diagnostic information in situations which might otherwise require exploratory laparotomy. JAMES HALLS, MD

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Clinical Assessment of Left Ventricular Regional Contraction Patterns and Ejection Fraction by High-Resolution Gated Scintigraphy

AN IMPROVED, noninvasive, radionuclidic, gated blood-pool imaging technique has been developed for clinical analysis of regional contraction abnormalities of the left ventricle and determination of ejection fraction. The principal innovations include high-resolution collimation, higher information density, improved method for dynamic aortic-mitral-diaphragmatic border delineation, accurate selection of the end-systolic gating interval through the use of phonocardiograms and accurate end-diastole by on-line gating immediately following the electrocardiographic QRS. The results of scintigraphic studies were compared with selective radiopaque cineangiographic findings in 27 patients with cardiac disease; there were excellent correlations of ejection fractions ($r=0.93$) and abnormal contraction patterns (17/17 patients). In addition, the clinical usefulness in evaluating ventricular performance was shown in 79 patients with acute and chronic coronary artery disease. This radionuclidic technique allowed assessment of reversibility of segmental dyssynergy by the response to nitroglycerin in 20 patients. These findings illustrate the validity of this improved radionuclidic technique in the atraumatic quantification of ventricular function and suggest its usefulness in a variety of clinical conditions.

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Endoscopic Retrograde Cholangiopancreatography: An Update

IN RECENT YEARS, endoscopic retrograde cholangiopancreatography (ERCP) has been the subject of numerous enthusiastic reports and the success rate in five recent reviews was close to 90 percent. Indications for its use include jaundice of undetermined origin, suspected or known pancreatic disease and abdominal pain of suspected biliary or pancreatic origin.

Sepsis is a dangerous complication and many centers now use prophylactic antibiotics, either given parenterally or added to the contrast medium.

A transient rise in serum amylase occurs in most patients, particularly if an acinar "blush" or urogram occurs during filling. However, the clinical picture of acute pancreatitis is rare and two large surveys in this country report an incidence of 1 percent and 1.3 percent.

ERCP is primarily a radiographic procedure depending heavily on radiographs of the highest quality. Contrast medium usually drains rapidly from the pancreatic ducts and films have to be taken with the endoscope and cannula in place. This places an added responsibility on the radiologist to obtain diagnostic films under less than ideal circumstances. On the other hand, contrast medium remains in the biliary tree after removal

of the endoscope, allowing a more leisurely examination in a variety of positions.

The radiographic appearances of established chronic pancreatitis are usually typical; however, in patients with recurrent attacks of acute pancreatitis the ductal system may be within normal limits or show only subtle changes.

Making a distinction between carcinoma of the pancreas and chronic pancreatitis is often difficult, requiring careful assessment of the radiographic evidence in the light of clinical findings. Carcinoma of the papilla on the other hand, usually can be diagnosed by direct vision and biopsy studies.

ERCP usually can distinguish medical from surgical causes of jaundice, but "skinny needle" percutaneous transhepatic cholangiography is simpler and less disturbing to the patient and has a low complication rate. In cases of jaundice with a suspected pancreatic cause, ERCP has the advantage of being able to outline both duct systems.

More recently, opacification of the biliary tract, with the patient in a 20° head-down position, has allowed identification of intrahepatic discases such as cirrhosis and hepatic tumors.

Endoscopic sphincterotomy using diathermy has proved to be extremely safe and often results in the sponstaneous passage of retained stones after cholecystectomy. Dormia baskets and balloon catheters also have been used with remarkable success.

Thus, the widening application of ERCP has opened exciting new fields in both the diagnosis and treatment of pancreatic and biliary tract disease. The clinical value of some of these applications has already been established while others await more careful evaluation.

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The Role of Computed Tomography in Acute Head Trauma

SINCE Hounsfield's and Ambrose's initial work, computed tomography (CT) has gained widespread acceptance in the evaluation of intracranial pathology. CT is especially useful and accurate in the detection of intracranial hemorrhage, especially in acute situations. At our institution, angiography is used only rarely in cases of head trauma: In a series of 1,000 patients, CT scanning was done in 316 patients (32 percent) and abnormalities were shown in 51 percent of cases; angiography was done in only 35 of the patients (3.5 percent), mostly preceding CT scanning or when pathologic conditions unrelated to trauma (tumors, aneurysms, infection) were suspected.

Some of the advantages of CT over other modalities used to diagnose head trauma (angiography, echography and radionuclide studies) are (1) the rapidity and ease of single or multiple examinations; (2) the low mortality and morbidity, especially since iodinated contrast materials are used rarely in head trauma cases; (3) the accurate evaluation of complications of intracranial hemorrhage, such as hydrocephalus, porencephaly and other structural changes; (4) the differentiation of intracerebral hematoma from contusion/edema, an important neurosurgical distinction, and (5) the detection of surgically correctable lesions in seemingly nonsalvageable cases, such as in "brain stem contusion" patients.

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Pancreatic Pseudocyst: Total Evaluation

PSEUDOCYST OF THE PANCREAS may be a far more common sequela of pancreatitis than previously suspected from the more conventional radiographic methods of the past. With the advent of computed tomography and ultrasound, direct, noninvasive imaging of the pancreas is possible with discrete delineation of pseudocysts in and around the pancreatic bed.

Ultrasound is the method of choice in screening when pancreatic pseudocyst is suspected; it is less expensive, causes no known morbidity at the diagnostic energy levels used and does not expose the patient to radiation. Pseudocysts are dynamic lesions, and serial examinations with ultrasound are easily accomplished. Although with ultrasonography anatomic detail is not as precise as

with computed tomography, scanning can be done in longitudinal, transverse and oblique planes for excellent localization.

The main difficulties in visualizing a pseudocyst with ultrasound are extensive bowel gas which prevents adequate sound transmission, obesity, residual barium, and open wounds over the area of interest which prevent surface contact with the transducer. In these instances, computed tomographic scanning can yield excellent anatomic detail of the pancreas and adjacent anatomy, but in transverse tomographic sections only. Oral or intravenously given contrast material may be used to advantage with computed tomography to enhance the delineation of the pseudocyst. Computed tomographic scans are not degraded by bowel gas or obesity, but adequate delineation of the pancreas in cachectic patients may be difficult because of the lack of fatty tissues outlining organ boundaries. Acutely ill patients unable to suspend respiration are also not ideal candidates for computed tomographic scanning.

In summary, both computed tomographic scanning and ultrasound are excellent modalities in the detection of pancreatic pseudocysts and are complementary diagnostic techniques.

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Optimal Therapy for Rectal Cancer

CARCINOMA OF THE RECTUM constitutes a significant percentage of colorectal cancer, the most common lethal human malignancy. Despite aggressive surgical approaches (usually abdominoperineal resection), local recurrence in the perineum and pelvis is a common sequel, often without life threatening distant metastasis. These recurrences or persistences of tumor usually produce symptoms and complications which make life quite miserable for the patient, are very difficult and frustrating for the physician or surgeon to treat, and are generally impossible to cure.

It is possible, however, to predict which patient is likely to have a local recurrence, and with properly administered radiotherapy to these selected patients postoperatively, to prevent local recurrence. If the carcinoma extends through the entire extent of the bowel wall or there are regional lymph nodes involved (or both), the patient is at risk for local or regional recurrence. If the tumor is confined to the bowel wall and the regional nodes are negative, the risk is low.

Several studies now have shown that postoperative radiotherapy, given at a time when there are few remaining neoplastic cells, can greatly reduce the incidence of local recurrence in these high risk patients. Consequently, patients at risk for local recurrence with rectal cancer should be referred to a radiotherapist postoperatively.

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The Vestibular Aqueduct in Meniere Disease

RADIOLOGIC VISUALIZATION of the vestibular aqueduct in Meniere disease has received attention that probably is not warranted. The vestibular aqueduct is the bony canal within the temporal bone that leads from the vestibule to a fold of dura along the posterior inferior margin of the temporal bone. It contains the endolymphatic duct. Nonvisualization of this bony canal on tomography implies occlusion and has been mentioned as the cause of Meniere disease. Unfortunately the cause and effect relationships of Meniere disease are not quite that simple.

The probable explanation of nonvisualization of the vestibular aqueduct on tomography may well be related to the degree of pneumatization of the temporal bone. Temporal bones may be classified as well pneumatized, average pneumatization, and sclerotic in appearance. The course of the vestibular aqueduct is strikingly different in the three types of temporal bones with the vestibular aqueduct being very short and "C"-shaped and hence more difficult to see in the more sclerotic bones.

The temporal bones of patients with Meniere disease and chronic otitis media tend to be of

the sclerotic type. Oigaard compared the rate of visualization of the vestibular aqueduct in patients with Meniere disease, in patients with chronic otitis media and in normal persons. The patients with chronic otitis media and those with Meniere disease have similar rates of nonvisualization (51 percent versus 57 percent) whereas in normal persons nonvisualization was only 5 percent.

Meniere disease is probably related to abnormal physiology in the function of the endolymphatic duct and sac with poor resorption of fluid but it does not necessarily follow that bony changes also occur. Present evidence indicates that the bony canals (vestibular aqueduct) are perfectly normal and their configuration changes with the degree of development and pneumatization of the temporal bone. The role of radiology is to rule out acoustic neuromas or other lesions masquerading as Meniere disease.

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Guided Percutaneous Needle Aspiration of Retroperitoneal and Abdominal Masses

PERCUTANEOUS NEEDLE ASPIRATION TECHNIQUES, which have been employed successfully in evaluating intrapulmonary neoplastic and infectious lesions, now have been applied in the evaluation of intra-abdominal masses. The technique consists of localizing the intra-abdominal mass by a variety of radiologic methods, including fluoroscopy, angiography, ultrasound and computed tomographic scanning, to allow accurate placement of the needle in order to increase the chances of adequate sampling of the abnormal tissue. The biopsy specimen must be carefully handled and prepared, and an experienced cytopathologist must be available to provide accurate interpretation of the small amounts of tissue obtained by this technique.

Current experience indicates that a fine, 23-gauge spinal-type needle should be used because it has been shown that such a needle can traverse a variety of intra-abdominal organs, including hollow viscera, with no apparent deleterious side effects. (An 18- or 20-gauge thin-walled spinal needle is usually used for percutaneous pulmonary aspiration.) One study indicates an overall diagnostic biopsy yield of 85 percent of cases, without clinical complications.

Proposed indications for this technique include obtaining a histologic diagnosis without surgical operation, the staging of neoplastic diseases and facilitating treatment planning. This technique has been successfully applied to diagnose pancreatic masses, retroperitoneal lymph nodes, and other intra-abdominal and retroperitoneal soft tissue masses.

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Computed Tomography of the Adrenal Glands

COMPUTED WHOLE BODY TOMOGRAPHY is a noninvasive method of directly imaging the adrenal glands. The high resolution and density discrimination of computed tomography (CT) allows precise delineation of adrenal size, shape and position in almost every patient. The adrenal glands appear as small structures of tissue density surrounded by retroperitoneal fat on computed tomographic cross sections of the abdomen.

Normal adrenal glands may be imaged by computed tomography in more than 85 percent of patients. It is only when there is pronounced loss of retroperitoneal fat or when the patient is unable to suspend respiration or has excessive bowel motion during the CT scan that the adrenal glands are inadequately visualized.

Computed tomography of the adrenal glands in patients with suspected adrenal abnormalities provides information heretofore not easily obtainable. In patients with Cushing syndrome computed tomography has shown bilaterally enlarged but normal shaped adrenal glands in instances of bilaterial adrenal hyperplasia. Unilateral adrenal enlargement with distortion of the normal adrenal configuration is found in patients with an adrenal adenoma, carcinoma or cyst. In the evaluation of patients with hypertension, computed tomography of the adrenals has shown both bilateral and unilateral pheochromocytomas and made it pos-

sible to detect cystic degeneration of these adrenal tumors. Alteration in the configuration of the adrenal gland has been shown in patients with hyperaldosteronemia secondary to small adrenal adenomas and in cases of adrenal metastasis. Computed tomography also provides information about the extent of adrenal abnormality and for determining if disease has spread to the liver or retroperitoneal structures.

Because conventional techniques of imaging the adrenal gland all have distinct disadvantages, computed tomography would appear to be the method of choice in the initial evaluation of suspected adrenal abnormalities. A normal study would virtually exclude an adrenal mass lesion, while detection of an adrenal abnormality may indicate the need for further more invasive diagnostic procedures such as adrenal angiography or venography.

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EDITORIALS

Health Systems Agencies and Local Physicians

It is safe to assume that relatively few physicians and less of the public are more than vaguely aware of the National Health Planning and Resources Development Act of 1974 (PL 93-641) or of the proposed Health Planning and Resources Development Amendments of 1978 (HR 10460) now being considered by the Congress. Everyday patient care and professional practice will be profoundly influenced by the way this law is implemented and its reach no doubt extended. If the federal strategy (to use a federal term) succeeds, the local Health Systems Agencies (HSA's) will have a great deal to say about local planning for health care and the expenditure of federal funds for health in their area.

PL 93-641 grew out of three former federal programs and combined and strengthened them. These were Comprehensive Health Planning, Regional Medical Programs and the Hill-Burton Act. PL 93-641 divides all of the United States into health service areas (also HSA's). Within each area it sets up a Health Systems Agency (HSA). The local HSA is a regional or area agency which may be a private nonprofit corporation, a unit of local government, or part of a public multipurpose planning agency. Each HSA has a fulltime staff, paid by the federal government, who collect and analyze data and make recommendations to the HSA governing body. An HSA executive committee or governing body is made up of 20 to 30 members. Consumers must be in the majority. In addition several categories of "providers" must be represented in the nonconsumer portion. It works out that the slots for practicing physicians are quite limited, perhaps one or two on each HSA governing body. The same mix applies to all the HSA councils and committees as well.

The local HSA's are now in various stages of development throughout the nation. At the same time something of a four-way power struggle seems to be going on within government. The Congress perceives the power to lie in the consumer-dominated local HSA's, with federal guidelines to help them. The federal bureaucracy in the Department of Health, Education, and Welfare, responsible for developing the regulations, sees the federal guidelines more as federal mandates to be followed by the local HSA's. The state governments under the law have a role in coordinating statewide HSA activities and steering HSA's toward statewide goals, and they are presently jockeying with the federal government for the power to do this. And lastly, many local governmental authorities are seeking as much dominance and control of local HSA's as possible. So once again we seem to be embarked upon a massive, complicated and costly federal health program which is based upon a theoretical hypothesis which has never been tested and may or may not ever work. The potential for havoc is great, but there is also potential for good, for a more rational approach to health care at the local level, with some coordination at the state level and some help and guidance from the national level.

The omission, almost to the point of exclusion, of a significant presence of practicing physicians at each level of planning and decision making under this law seems to be a flaw which may prove serious and could even be fatal. There are great expectations of the conventional wisdom of the consumer and of the knowledge and expertise of other "providers" of health care. Yet it is the physician who in many ways is the most knowledgeable person of all about much of what is involved, and physicians are in a position to give expert counsel and advice which may or may not be sought, or listened to.

It is worth emphasizing that the HSA's may actually be ushering in a new period of participatory democracy in health care. This may prove to be the wave of the future. At present it is an experi-

ment with little accumulated experience with how it will work or even if it can be made to work. Physicians have been assigned a peripheral rather than a central role. But if this is indeed to be the wave of the future for health care in this nation, physicians had best prepare to adapt; that is, find ways how to participate effectively in the deliberations of the HSA's at the various levels. This will be a new dimension of medical practice which will require new approaches and new applications of what may be old skills. Since in a very real sense the HSA's will have health care problems, the aim will be for local physicians to participate in these democratic processes, especially at the local level, in much the same way they guide, teach, advise and help any of their patients who have health care problems. And, as is so often the case in other forms of medical practice, this will often be wearing, time consuming and frustrating. But it is essential that knowledgeable practicing physicians become involved in these matters of health and health care. Those who do this and do it successfully will often be rendering service to their profession and to the public well above and beyond the traditional call of duty. In retrospect they may even prove to have been the medical heroes of this moment in the evolution of health care in this nation.

—MSMW

Diagnosing Megaloblastic Anemias

IN THIS ISSUE Carmel reviews the laboratory diagnosis of megaloblastic anemias, emphasizing well-established, reasonably accessible laboratory tests. Another excellent review of the diagnostic approach to megaloblastic anemia is that of Chanarin,[1] published in an issue of *Clinical Haematology* devoted entirely to the megaloblastic anemias. Like Chanarin, Carmel stresses the importance of an elevated mean corpuscular volume (MCV) (that is, macrocytosis) in "tipping off" the diagnosis of megaloblastosis. An important fact which should also be mentioned is that the megaloblastic red cell is not only large but also oval; that is, it is a macroovalocyte. Its oval character distinguishes it from those large red cells that occur in hypothyroidism, in aplastic anemia, in liver disease not associated with vitamin deficiency and in various hemolytic anemias.[2]

Carmel notes that the question is unsettled as to whether subtle vitamin deficiency may explain the neutrophil hypersegmentation which has been reported in iron deficiency. We believe this question may have finally been laid to rest by our recent findings[3,4] that almost invariably there is underlying folic acid deficiency in iron deficient patients with neutrophil hypersegmentation.

A particularly interesting very recent finding is the report by Clarkson and Mockridge at the American Society of Hematology Annual Meeting in San Diego in December 1977[5] that one of the earliest events in the development of folate deficiency is a reticulocytopenia and a macroreticulocytosis which is present before the mature red cells become large, and which is accompanied by a low serum folate level, but occurs before the mean red cell folate becomes low.

Carmel notes that the white cell changes in so-called erythroleukemia, more accurately described as DiGuglielmo syndrome or preleukemia, tend to be less classical. Actually, it is a striking fact that in this syndrome there may tend to be hyposegmentation rather than hypersegmentation.[2] This seems to be analagous to the pseudo-Pelger-Huet anomoly which occurs in about 10 percent of patients with myelogenous leukemia at one time or another during their clinical progression.

The Carmel review of serum and red cell folate indicates that much depends on how one chooses to define deficiency. Perhaps it would be clarifying to quote verbatim from conclusion number two of the Proceedings of the Workshop on Human Folate Requirements, published in 1977:[6]

> What constitutes appropriate assessment of nutritional status with regard to folate? Answer: Measurement of serum plus red cell folate appears to be the most practical approach. Current evidence suggests that, when serum and red cell folate are both low, other more direct indices of folate deficiency will be present (i.e., a low liver folate and a bone marrow "dU suppression" test demonstrating subnormal DNA synthesis by bone marrow cells correctable by adding folate or methylfolate *in vitro*). Measurement of tissue folate (i.e., red cell or liver folate) alone is not adequate because deficiency of vitamin B_{12} results in low tissue folate (but not low serum folate). Low serum folate alone is not adequate as a test for folate deficiency because it is too sensitive; i.e., serum folate is low after only three weeks of folate deprivation, which is months prior to exhaustion of tissue folate stores and development of biochemical folate deficiency.

As Carmel notes, in the first few days after folate therapy, red cell folate is still low and it still can be used to determine that folate deficiency was present. More recent studies indicate

that the lymphocyte dU suppression test may show the prior existence of folate or B_{12} deficiency as much as two months after vitamin therapy has been instituted.[7]

One can create in one's own laboratory, or purchase commercially, a kit capable of doing radioassay for both vitamin B_{12} and folic acid simultaneously, for roughly the cost and time of doing just one assay.[8]

One is inclined to agree with Carmel that the therapeutic trial is occasionally still of clinical utility. When it is done, the dose of folic acid should be 100 μg per day, and, when it is done with vitamin B_{12}, the dose should be 1 μg per day.[2]

Now that it is becoming clear that iron deficiency is present in a third to a half of all patients with megaloblastic anemia,[2] there are those who say that the old "shotgun therapy" approach was right all along. Not so. There was never anything wrong with "shotgun therapy," provided that one first made the correct diagnosis or diagnoses by appropriate testing. Such remains true today. If one draws blood for serum and red cell folate levels, serum vitamin B_{12} level, and does appropriate diagnostic tests for iron deficiency, then there is probably not much wrong with at that time starting "shotgun therapy" if one really wishes to. One can then be guided by the laboratory results as to what the deficiencies really are, and how the patient should properly be treated. "Shotgun therapy" without diagnostic evaluation first is as deplorable today as it was 40 years ago. Of course, if "shotgun therapy" is used, it may or may not be possible to diagnose a covert nutritional deficiency that is less severe than the most dominant deficiency.

Detection of malabsorption of vitamin B_{12} due to gastric or intestinal dysfunction[9] should include recognition of the important finding by Doscherholmen and Swaim[10] that the absorption of crystalline radioactive vitamin B_{12} may be normal in elderly people who subnormally absorb vitamin B_{12} from their food due to their hypochlorhydria or achlorhydria.

To the many possible causes of folate deficiency discussed by Carmel and by others,[2] must be added congenital defective transport of folate across cell walls.[11]

To the Carmel suggestion that reevaluation should be done in patients after therapy one can only say, "Amen," and add that one month after the start of vitamin therapy, reevaluation should be carried out in every patient with megaloblastic anemia for hidden iron deficiency which may only be measurable after the vitamin deficiency has been treated.[2]

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A Study of Potentially Compensable Events

ONE OF THE worthwhile results of the recent malpractice crisis in California was the decision of the California Medical Association and the California Hospital Association to sponsor the Medical Insurance Feasibility Study which is reported elsewhere in this issue. This objective study of 20,864 hospital charts from 23 representative hospitals in California developed a significant new method for measuring the frequency, causes and potential tort liability of adverse outcomes to patients in the course of health care management. The new measurement techniques which were created not only provide the most accurate information so far available, they also will be of great value in future applications.

The data are impressive. They are at once a measure of the relative safety and success of modern scientific medicine in the hospital setting where the risks are often great, but at the same

time it is sobering to realize the absolute number of misadventures that actually do occur. However, it is to some degree reassuring to find that the percentage of potentially compensable events is quite small when one realizes that all diagnosis and treatment in medicine carry a greater or lesser risk. But perhaps the greatest significance of this study is that it addresses a social, economic and very human problem of medical care in an objective and scientific fashion—and this is indeed refreshing.

—MSMW

Prognostic Determinants in Chronic Hepatitis B Infection

A Reevaluation

RATIONALES for the diagnosis and therapy of patients with chronic hepatitis have improved in recent years as serologic markers have been discovered which permit identification of the infective virus,[1] and as attempts have been made to establish standard morphologic criteria in liver biopsy specimens which would predict prognosis.[2-4] Nevertheless, despite these advances, some patients with chronic hepatitis are not readily classifiable into clinical subgroups and are perplexing diagnostic and therapeutic challenges. Usually these "problem" patients are hepatitis B surface antigen (HB_sAg)-positive since hepatitis A is frequently self-limiting and does not result in cirrhosis,[5] while patients with HB_sAg-negative chronic hepatitis most often have recognizable histologic features which predict a favorable response to corticosteroid therapy. However, in some patients with chronic HB_sAg-positive infection, the morphologic determinants of prognosis seem less reliable, and there is growing uncertainty about the efficacy of corticosteroids.[6,7]

Elsewhere in this issue, a Specialty Conference is presented from the Hepatology Division and Department of Pathology of the John Wesley County Hospital, Los Angeles, which reviews a number of clinical, epidemiologic, pathologic and therapeutic aspects of chronic hepatitis B virus (HBV) infection. This center has had an extensive experience and their long-term observations have helped to delineate some special problems that occur with this form of hepatitis, and to direct attention to additional features of this disease which may be useful in judging prognosis and choice of therapy. What are some of these problems? What determinants of prognosis are most useful clinically in the HB_sAg-positive patient? First, the findings on liver biopsy, which are generally regarded as the cornerstone of diagnosis and management in patients with all types of chronic hepatitis, may occasionally be misleading in HBV infection. They are most useful in identifying chronic persistent or unresolved viral hepatitis which are benign and nonprogressive forms of chronic HBV infection. Liver biopsy findings also readily identify patients with bridging necrosis or an advanced cirrhosis, even though sampling error may prevent accurate assessment of its extent.[8] However, in many cases the morphologic features may be more difficult to interpret. Often focal areas of portal fibrosis or nodularity are seen although there is no generalized loss of architecture. Fibrous septae may bridge portal triads in some lobules but not in others and there may be an increase in inflammatory cell infiltrate and spotty or "piecemeal" periportal necrosis and fibrosis. Usually, however, central-portal bridging is absent. The process may wax and wane with time and even vary considerably in different areas of the same biopsy specimen.[9] Pathologists usually classify this example as chronic active hepatitis according to earlier international criteria,[10] which carried with them the clinical expectation that the chronic hepatitis would progress to a cirrhosis and that the process would be arrested with steroids. The recent experience of the John Wesley Hospital hepatologists and pathologists, as well as others, is that neither of these conclusions may necessarily be correct, particularly if the patient has chronic HB_sAg-positive hepatitis.

If the liver biopsy findings cannot always be relied upon to determine prognosis, are there other clinical findings that might be helpful in identifying those patients who are likely to progress to cirrhosis? Since a young asymptomatic male with chronic active hepatitis frequently has a relatively nonprogressive illness, the patient's age and sex and whether or not he has symptoms may be important. Age has long been recognized to influence the response to hepatitis infection, although the reasons have never been fully elucidated.[11] Changes in immune response to the HBV infection or relative impairments in the regenerative response have been offered as possible explanations. Dr. Peters has called this "the impaired regeneration syndrome" emphasizing that older

patients either die of progressive hepatic failure a few months after the onset of severe HB_sAg-positive hepatitis or eventually recover.[9]

However, most patients with advanced HB_sAg-positive cirrhosis (and this includes those patients with HB_sAg-positive disease associated with hepatocellular carcinoma) do not have any antecedent history of acute hepatitis. Anicteric viral hepatitis has long been recognized as a precursor of cirrhosis[12] and most patients with viral subacute hepatic necrosis in whom postnecrotic cirrhosis develops have had insidious onsets rather than typical acute hepatitis syndromes.[3] These differences in clinical presentations suggest that the immune response to HBV infection may be a critical determinant in the eventual outcome of the disease. Gudat and co-workers showed that there may be different fluorescent antibody patterns to HBV surface antigen and core antigen in liver cells in different clinical forms of HBV infection which may reflect a difference in the immune response.[13] They observed that patients with chronic active hepatitis have persistence of both core and surface antigen in hepatocytes bordering areas of cell necrosis and collapse, and that the persistence of core antigen near zones of collapse correlated with progressive disease in these patients (Bianchi, personal communication). Careful clinical-pathological correlations of this type may eventually determine whether fluorescent antibody studies of liver biopsy material will be helpful clinically.

Wedged hepatic vein pressure measurements (WHVP) and peritonoscopy are two other approaches that are being used by the Los Angeles group to help determine the extent and severity of the liver damage in HB_sAg-positive chronic active hepatitis. As illustrated by the case discussion, a progressive increase may be an early indication that cirrhosis is developing. Since elevations in WHVP are unusual in viral hepatitis this measurement may be useful.[14] However, further morphological and physiological correlations are needed, before WHVP can be accepted in routine clinical care. Peritonoscopy provides additional information about liver size and surface nodularity but may not necessarily accurately reflect hepatic functional mass. This technique, like WHVP, is invasive and requires a skillful operator with experience. A critical comparison of results of peritonoscopy with conventional diagnostic techniques is also needed before this potentially useful approach can be more widely accepted. There is also a need to develop noninvasive tests of liver function such as the ^{14}C-aminopyrine breath test which can accurately reflect changes in the mass of functioning hepatic tissue and which could be used to assess the natural history of chronic forms of liver disease, and their response to therapy.[15]

If these studies show that cirrhosis is developing in a patient with chronic HB_sAg-positive hepatitis, will corticosteroids benefit such patients? As Dr. Reynolds suggests, it may be several years before this question can be definitely answered although the Los Angeles group would probably vote no. However, caution must be exercised in interpreting the results of steroid therapy from different medical centers. Therefore the outcome of steroid trials in Los Angeles may differ from those in the Mayo Clinic or in London if the patient population is dissimilar. Could the poor response to steroids in Los Angeles reflect a difference in the natural history of disease since a large percentage of patients may have acquired HBV through drug abuse? Many are males and relatively asymptomatic and such patients are often unresponsive to steroid therapy. Experience elsewhere has been variable with older patients who are clinically ill, and who have more extensive histologic abnormalities including bridging necrosis or active cirrhosis. Some claim that steroids are effective but less frequently than when the HB_s antigen is negative.[16,17] A Mayo Clinic study suggests that HB_sAg-positive patients who are "e" antigen positive[18] may not respond to steroids, while those with antibody to "e" antigen do. A recent preliminary report suggests that circulating core antigen may be detected more frequently than "e" antigen and correlates more closely with deterioration and death than the presence of "e" antigen.[19]

Obviously more data are needed to more clearly define subpopulations of HB_sAg-positive patients with chronic active hepatitis before reaching a final judgment on the use of corticosteroid in this disease. No alternative treatment is immediately forthcoming, although trials with interferon and antiviral agents should and are receiving increased attention. Until then, corticosteroids should be used judiciously in HB_sAg-positive patients and reserved primarily for those with chronic active hepatitis who are over 40, are symptomatic, have biochemical evidence of significant activity and in whom liver biopsy findings show features consistent with progressive forms of chronic active hepatitis.[8] In view of the seriousness of potential

side effects, prolonged use of corticosteroids should be carefully avoided particularly if they do not elicit a clinical or biochemical response after several weeks of therapy. The problem is well illustrated by the patient in this month's specialty conference in whom cirrhosis and ascites developed despite a trial of corticosteroids.

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CASE REPORTS

Refer to: Laiken S, Beck CH Jr, Timms RM: Acute renal failure associated with hemodialysis and hypophosphatemia. West J Med 128:343-345, Apr 1978

Acute Renal Failure Associated With Hemodialysis and Hypophosphatemia

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In recent years the significance of hypophosphatemia has been increasingly recognized.[1,2] Several authors have noted a hemolytic anemia produced by hypophosphatemia.[3,4] Here, a case will be described in which hemolysis occurred during hemodialysis for salicylate overdose and led to acute renal failure in a patient subsequently found to be severely hypophosphatemic.

Report of a Case

The patient was a 50-year-old white man who arrived in the emergency room comatose after transfer from another hospital where the diagnosis of salicylate intoxication was made. After speaking with the patient's family it was learned that he suffered from a poorly defined low back pain and had been ingesting increasing doses of aspirin over the 48 hours before admission. Although it was not known at the time of admission it was subsequently found that he also had been consuming daily an estimated two quarts of magnesium aluminum hydroxide containing antacid, for known peptic ulcer disease. Initial and follow-up history indicated that he had not been exposed to heavy metals or other nephrotoxins.

On physical examination the patient was obtunded and appeared older than his stated age. Blood pressure was 150/100 mm of mercury, heart rate was 90 beats per minute with regular rhythm and there were 25 deep respirations per minute. Jugular venous pressure was normal by inspection. The chest was clear and results of cardiac and abdominal examinations were unremarkable. Neurological evaluation showed cranial nerves 2 through 12 to be intact. The deep tendon reflexes were normal and bilaterally symmetrical. There was no Babinski sign. The patient reacted to painful stimuli and was able to move all extremities. He was unable to follow most simple commands, could not sit up and was unaware of the presence of others.

Laboratory studies gave the following values: salicylate level, 90 mg per dl; serum sodium, 150 mEq per liter; chloride, 115 mEq per liter; potassium, 3.5 mEq per liter; bicarbonate, 17 mEq per liter; blood urea nitrogen, 20 mg per dl; creatinine, 1.3 mg per dl; albumin, 3.8 grams per dl, and serum glucose, 136 mg per dl. Arterial blood gas studies showed an oxygen pressure of 89 mm of mercury, a carbon dioxide pressure of 16 mm of mercury and a pH of 7.39 on room air. Hematocrit was 32 percent; hemoglobin, 10 grams per dl; leukocyte count, 12,100 cells per cu mm; prothrombin time, 13.9 seconds with control of 11.4 seconds; platelets were normal by smear, and the red blood cell indices were hypochromic and microcytic. The patient's stool was positive for occult blood. Toxicology screen was negative except for salicylate.

The patient was initially given 25 mg of vitamin K_1 intramuscularly, an infusion of 5 percent glucose with normal saline, 150 mEq of sodium bicarbonate, and one dose of acetazolamide, 250 mg given intravenously. Because of the patient's high salicylate level and poor clinical status, it was elected to lower the salicylate level by hemodialysis. Silastic catheters were placed in the femoral veins bilaterally by the Seldinger technique. Dialysis was carried out with regional heparinization using a Gambro Lundia Optima 17 cartridge for 3¼ hours with arterial blood flow of 215 ml per minute and dialysate flow of 500 ml per minute. Dialysate conductivity and temperature were within normal limits during the entire dialysis making hyposmolality of the dialysate unlikely. The dialysate from the dialyzer was Clinitest® negative and therefore thought to be formaldehyde free before the patient was treated.

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This treatment reduced the salicylate level to 40 mg per dl. Clear yellow urine was initially excreted at greater than 100 ml per hour. Midway through dialysis the urine abruptly became red brown and decreased in volume to less than 20 ml per hour. During this time there was no significant drop in arterial blood pressure or decrease in weight, and the calculated serum osmolalities before and after dialysis were 293 and 291, respectively. An analysis of urine showed numerous red blood cells, and 4 plus protein. The spun supernatant also was 4 plus for protein and strongly positive for occult blood. The patient's plasma was noted to be pink in color. All blood sent to the laboratory was reported as grossly hemolyzed including a sample with a phosphorus value of 2.3 mg per dl and a calcium level of 8.4 mg per dl. Eight hours after dialysis, the serum free hemoglobin was 125 mg per dl (normal less than 5 mg per dl for this laboratory). Despite a fluid challenge and a transient increase in urine output with 320 mg of intravenous furosemide, the blood urea nitrogen and creatinine values rose to 28 mg per dl and 2.6 mg per dl, respectively, eight hours after dialysis.

The serum phosphorus value 18 hours after the onset of oliguria was 0.4 mg per dl on a nonhemolyzed specimen. At the same time the serum free hemoglobin was 2 mg per dl. The hematocrit had decreased to 24 percent by 24 hours after dialysis. Consequently, a transfusion was then done with 4 units of banked packed red blood cells. The patient's blood urea nitrogen and creatinine values increased and the oliguria persisted for six days. Treatment was carried out with potassium hydrogen phosphate solution, raising the serum phosphorus level to 3.9 mg per dl. Thereafter, hemodialysis was carried out without complication. After a week the patient entered the diuretic phase of acute renal failure. Hemoglobin casts were noted in the urine. Within several weeks the blood urea nitrogen and creatinine values returned to normal. A glucose-6-phosphate dehydrogenase (G6PD) screen was obtained and showed the presence of enzyme. The P_{50} (partial pressure of oxygen at which hemoglobin is 50 percent saturated) was 21 mm of mercury before phosphate repletion and 48 hours after transfusion.

Discussion

The patient described here clearly underwent a hemolytic episode during hemodialysis. This produced acute hemoglobinuria and renal failure. To our knowledge such episodes have not been encountered with hemodialytic therapy for aspirin intoxication in the past. No such problem has been reported related to acetazolamide and bicarbonate therapy for salicylate poisoning.[5] A hemolytic reaction to one dose of acetazolamide seems unlikely because the drug will cause a pancytopenia rarely, but not hemolysis.[6] In addition, acute hemolysis secondary to sulfonamides evolves over a considerably longer time and is usually accompanied by a leukemoid reaction.[7,8] In this patient hemolysis occurred within four hours and the leukocyte count actually decreased to less than 10,000.

It appears likely that the hemolysis was secondary to hypophosphatemia. The initial result with a phosphorus value of 2.3 mg per dl on a grossly hemolyzed specimen is undoubtedly an overestimate, because hemolysis is known to falsely elevate the serum phosphorus value.[9] This is substantiated by the low serum phosphorus value (0.4 mg per dl) after hemolysis ceased. The clearance of phosphate with the dialyzer used is only 58 ml per minute for the given arterial and dialysate flows.[10] If this patient had a normal serum phosphorus before dialysis he would not have had sufficient dialyzer clearance capability or length of dialysis to lower the serum phosphorus to this level.[16] Alkalosis, especially respiratory alkalosis, is thought to be a cause of severe hypophosphatemia.[11] However, this patient was not alkalotic during the time covered by this report. Increasing the serum phosphorus to the normal range allowed subsequent dialysis without hemolysis.

The hypophosphatemia seen in this man was most likely due to chronic aluminum-magnesium hydroxide antacid abuse. This drug has been used experimentally to produce a phosphate depletion syndrome in human volunteers.[1] It is thought that the hemolytic anemia of hypophosphatemia is a result of increasing erythrocyte fragility with adenosine triphosphate depletion.[3] One would expect fragile erythrocytes to be particularly susceptible to hemolysis when subjected to passage through a hemodialyzer.

In addition to excessive antacid consumption, hypophosphatemia is known to occur in a variety of clinical situations, including acute and chronic alcoholism, sepsis and hyperalimentation with phosphate-poor solutions.[9] While a direct cause-effect relationship between hypophosphatemia

and hemolysis in relation to hemodialysis is not proven by this report, the circumstantial evidence is compelling. It seems prudent to obtain a serum phosphate value before hemodialysis of patients in whom hypophosphatemia is clinically suspected. Patients with severe hypophosphatemia could be readily treated in the hope of preventing hemolysis.

Patients with hypophosphatemia may be depleted of red cell 2,3 diphosphoglycerate.[12] Oxyhemoglobin dissociation was notably abnormal in this patient with a large leftward shift in the oxyhemoglobin dissociation curve. The abnormal P_{50} may have been caused by the severe hypophosphatemia aggravated by the transfusions with banked red cells probably already low in red cell 2,3 diphosphoglycerate. With hemolysis resulting in a sudden loss of hemoglobin, the combination of anemia and increased affinity of hemoglobin for oxygen could acutely threaten tissue oxygenation. This is further reason for recognition and early treatment of hypophosphatemia.

Summary

The clinical importance of hypophosphatemia has become increasingly recognized. A case of hemoglobinuric renal failure following hemodialysis of a severely hypophosphatemic patient is described. It is proposed that the increased erythrocyte fragility of hypophosphatemic patients may predispose them to hemolysis during hemodialysis and the importance of correcting serum phosphate concentration in such patients is stressed.

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Refer to: Daskalakis MK: Fibromuscular hyperplasia of external iliac arteries. West J Med 128:345-347, Apr 1978

Fibromuscular Hyperplasia of External Iliac Arteries

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FIBROMUSCULAR HYPERPLASIA of the external iliac arteries may represent a part of the whole involvement of the arterial system or may represent a localized manifestation of the disease. Symptoms of the arterial insufficiency and clinical findings are related to the degree of stenosis, and impairment of blood flow. The purpose of this communication is to report such a symptomatic case and to review the surgical procedures which have been used for the management of patients with fibromuscular hyperplasia of external iliac arteries. To our knowledge, surgical approach with dilatation of the external iliac arteries has not previously been reported in patients with fibromuscular hyperplasia.

Report of a Case

A 52-year-old white man was admitted to West Anaheim Community Hospital on January 30, 1973, with a four-year history of intermittent claudication of both lower extremities. Physical examination gave the following findings: blood pressure, 140/85 mm of mercury; systolic bruit over both iliac arteries with radiation to both femoral arteries; notably diminished femoral, popliteal, posterior tibial arterial pulses and absent pedis dorsalis pulses bilaterally.

An aortogram showed typical changes of fibromuscular hyperplasia of external iliac arteries bilaterally (Figure 1). Surgical operation was carried out on February 7, 1973, under general anesthesia and dilatation of the iliac arteries, bilaterally, was done through bilateral groin incision and transverse arteriotomies of common femoral arteries. Bakes dilators, sizes 3 to 9 mm, were used progressively with some resistance en-

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countered passing the dilator through the proximal part of the external iliac arteries. An aortogram (Figure 2) done following the dilatation showed pronounced improvement. Postoperative course was uneventful. Pulses returned to normal, the systolic bruit over the iliac arteries was gone and symptoms of intermittent claudication were entirely relieved. Aortograms done on February 18, 1975 (Figure 3), showed no evidence of fibromuscular hyperplasia. The patient was seen in March 1977; there were normal pulses and no bruits and he continues to be asymptomatic.

Discussion

Fibromuscular hyperplasia of the external iliac arteries has been reported as coincidental findings during arteriographic studies.[1-3] When, however, the stenotic lesions become dynamically significant, then symptoms of arterial insufficiency with intermittent claudication will appear,[4] as in the case report here.

Arteriographic studies have been used to determine the extent and severity of the lesion, the appearance of which is pathognomonic and looks like corrugated Dacron® graft with some areas more stenotic than others. Dotter and Judkins have introduced the closed dilatation technique in patients with arteriosclerotic occlusive disease of the iliac and femoral arteries.[5,6] Lately, the open dilatation technique, using rigid metallic dilators, has been used successfully in treating patients with fibromuscular hyperplasia of carotid[7] and renal arteries.[8]

Segmental resection with saphenous vein graft replacement[4] has given good results. Since the lesion is segmental, in the external iliac artery, other techniques such as resection with Dacron graft replacement or bypass procedure using Dacron or saphenous vein graft, are expected to have good, lasting results.

Open dilatation technique was used in our case. It is simple; using a transverse common femoral arteriotomy with gentle introduction of Bakes dilators, the areas of stenosis were dilated. It can be done under local anesthesia.

The patient's symptoms of intermittent claudication were entirely relieved, the systolic bruit over the iliac arteries disappeared and the pulses of the lower extremities returned to normal. Arteriograms done 24 months later showed no evidence of fibromuscular hyperplasia of the external iliac arteries.

It is believed that the histopathology of the fibromuscular hyperplasia involving medium and

Figure 1.—Preoperative aortogram showed the involvement of external iliac arteries.

Figure 2.—Operative aortogram immediately after dilatation of external iliac arteries.

small size arteries is such that dilatation techniques using rigid metallic dilators will give good, lasting results in patients with this clinical syndrome.

Summary

Fibromuscular hyperplasia of external iliac arteries may produce symptoms of arterial insufficiency of lower extremities. Our experience emphasizes the technical advantages of an alternative, simpler surgical procedure such as open dilatation of the external iliac arteries through common femoral arteries using metallic rigid dilators.

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Figure 3.—Aortogram 24 months following operation showed no evidence of fibromuscular hyperplasia.

Refer to: Yassinger S, Midgley RC, Cantor DS, et al: Retroperitoneal emphysema after colonoscopic polypectomy. West J Med 128:347-350, Apr 1978

Retroperitoneal Emphysema After Colonoscopic Polypectomy

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BLEEDING AND PERFORATION are the most common complications of colonoscopic polypectomy.[1,2] Retroperitoneal emphysema, a rare complication of sigmoidoscopy, barium enema[3,4] and upper gastrointestinal endoscopy,[5] was recently reported as a complication of colonoscopy.[6] Two cases of widespread retroperitoneal emphysema that developed after colonoscopic polypectomy were recently encountered. One of these cases had pronounced subcutaneous and mediastinal emphysema as well. A description of this unusual complication of colonoscopic polypectomy in these two patients and an approach to its management form the basis of this communication.

Reports of Cases

CASE 1. A 61-year-old man reported to the emergency room because of an episode of hematochezia. Sigmoidoscopy showed only internal hemorrhoids. Subsequent barium enema examination showed polypoid lesion at the hepatic flexure. The patient was referred to the gastroenterology service for colonoscopy.

The patient was given 30 mg of alphaprodine (Nisentyl®) intravenously as an analgesic during the procedure. An Olympus CF-LB2 colonoscope was introduced into the rectum and advanced to the hepatic flexure area without difficulty. In the region of the hepatic flexure, a 1.5 to 2.0 cm diameter smooth pedunculated polyp was found. The colonoscope was advanced to the cecum and no further lesions were seen. The colonoscope

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was then withdrawn to the hepatic flexure and the polyp was excised with a coagulating snare without difficulty. Suction was applied to the excised polyp, but the initial attempt at removal from the colon was unsuccessful. The instrument was reinserted to the level of the polypectomy site which was observed not to be bleeding. After slow withdrawal of the colonoscope, the free polyp was found in the descending colon and successfully removed. The patient tolerated the procedure well and did not complain of discomfort following termination of the procedure. However, a large pneumocele was discovered on the abdominal examination after the procedure.

Shortly thereafter, the patient was found to have crepitation in the subcutaneous tissues of neck, thorax, abdominal wall and groin. Examination of the heart and lungs showed no abnormalities. The abdomen was mildly distended and tympanitic. Mild direct tenderness was found in both lower quadrants with no rebound tenderness and normally active bowel sounds. The scrotal sac was distended to 10 cm in diameter with air.

On x-ray examination of the abdomen, pneumoperitoneum with free air below the diaphragm was noted (Figure 1), and pneumoretroperitoneum with extensive retroperitoneal air. X-ray films of the chest showed subcutaneous emphysema of the neck and lateral chest wall with pneumomediastinum (Figure 2). Laboratory studies gave the following values: hematocrit, 40.3 percent; hemoglobin, 13.7 grams per dl; leukocyte count, 9,300 with 73 percent polymorphonuclear leukocytes, 13 percent bands, 8 percent lymphocytes, 2 percent monocytes and 2 percent eosinophils. Results of analysis of urine were within normal limits. Histologic examination of the excised polyp showed a submucosal lipoma with no evidence of malignancy.

The patient was prescribed a regimen of nothing by mouth and intravenous fluids. The pneumocele was decompressed with an 18-gauge needle. Twenty-four hours after colonoscopy, a temperature of 37.8°C (100°F) (orally) developed and the leukocyte count had increased to 14,300 with 63 percent polymorphonuclear leukocytes, 11 percent bands, 23 percent lymphocytes, 2 percent monocytes and 1 percent eosinophils. Peritoneal signs were absent. Intravenously given clindamycin and gentamicin were started with prompt resolution of the fever. Blood cultures drawn before institution of antibiotics were negative. Seven days after colonoscopy and six days after the institution of antibiotic therapy, resolution of the subcutaneous and retroperitoneal air was shown on x-ray films. Oral feedings were begun and the patient was subsequently discharged in good condition.

Case 2. A 71-year-old man, in whom multiple colonic polyps were found on a barium enema study in September 1975, was referred for colon-

Figure 1.—X-ray film of the abdomen (case 1) showing retroperitoneal air outlining both kidneys.

Figure 2.—X-ray film of the chest (case 1) showing subcutaneous air in the neck, pneumomediastinum and air under the diaphragm.

oscopy. Only one of the polyps was amenable to removal with the coagulating snare. Biopsy studies of other sessile polyps showed fragments of adenomatous and hyperplastic polyps. Atypical hyperplasia was found in one of the sigmoid colon polyps. It was elected to continue to observe the lesion and colonoscopy was repeated in April 1976.

The patient was sedated with 50 mg of intravenously given meperidine and 10 mg of diazepam. An additional 8 mg of diazepam was required during the procedure. An Olympus CF-LB2 colonoscope was passed without difficulty to the cecum where a filling defect was thought to be an inverted appendiceal stump. Biopsy specimens were taken of five small, less than 1 cm in diameter, sessile polyps at various levels of the colon and the polyps were fulgurated. A large 1 cm diameter polyp on a broad-based stalk, seen at the junction of the descending and sigmoid colon, thought to be suspicious for carcinoma, was removed with some difficulty using the coagulating snare. Because the snare had not cut completely through the polyp when completely closed, the polyp was placed against the instrument tip and the snare pulled until it cut through and released. An additional polyp in the sigmoid colon (8 mm in diameter) was also removed by snare cautery without problem. The sites of biopsy, fulguration and polypectomy were found to be unremarkable on reexamination. The patient tolerated the procedure well, except for complaint of abdominal pain when the snare was manually pulled through the large sessile polyp. The pain subsided within two to three minutes. Following the procedure, x-ray films of the abdomen were obtained because of the difficulty encountered with the removal of the suspicious polyp. Retroperitoneal air, a small amount of air below the right hemidiaphragm and air outlining the outer wall of a loop of small bowel were found.

Despite absence of peritoneal signs on examination, abdominal exploration for colonic perforation was felt indicated by the consulting surgeon because of the free intraperitoneal air. At surgical operation no definitive evidence of free perforation was found. Air in the leaf of the mesentery and a small serosal tear were seen in the rectosigmoid colon; the tear was closed with one 4-0 silk suture. There was no escape of gas in this area and no evidence that this was the site of perforation. Cultures of peritoneal fluid taken at surgery grew Escherichia coli. Administration of cephalothin intravenously, and later clindamycin, was instituted. The patient improved to the point that he was discharged on the ninth hospital day. Examination of the biopsy specimens taken at colonoscopy showed fragments of hyperplastic and adenomatous polyps. The polyps suspicious for carcinoma proved to be a submucosal lipoma and an adenomatous polyp.

Discussion

Fiberoptic colonoscopy is now a routine procedure in many communities, having gained widespread acceptance as a means of diagnosis and management of colonic diseases.[7-10] Utilization of flexible snares and electrosurgical current has revolutionized the approach to colonic polyps.[11,12] A recent summary of the literature on the complications of colonoscopic polypectomy showed that the incidence of perforation, bleeding and overall morbidity was less than 1 percent.[2] Retroperitoneal emphysema is a well-known but infrequent complication of sigmoidoscopy and barium enema,[3,4] and has been reported only once previously as a complication of colonoscopy.[6]

In case 1 and the previously reported case,[6] the procedure was done without technical difficulty. The first sign of a complication was the discovery of a large pneumocele followed by widespread subcutaneous emphysema. On the other hand, multiple snaring, biopsy studies and electrosurgical procedures increased the chance of encountering a complication in case 2. Since case 1 was managed nonoperatively and no obvious perforation of the colon was found at operation in case 2, the site of air leakage remains speculative. The most likely site of leakage in case 1 would appear to be below the peritoneal reflection since the air initially appeared in the scrotal sac. In case 2, air in the leaf of the mesentery and a small serosal tear were found in the rectosigmoid at operation, but no evidence was found that this was the site of perforation. Air insufflated during the procedure could have been forced through a small perforation at any of the biopsy or polypectomy sites. A small undetected rectal tear may have occurred in either case as a result of manipulation of the colonoscope. Air insufflation causing rupture of a small diverticulum is another possibility, but no evidence of diverticuli was observed at colonoscopy or on barium enema studies in either case.

Histologic examination of the polyp in case 1 and one of the polyps in case 2 showed a sub-

mucosal lipoma. Usually these neoplasms are not pedunculated, are easily recognized at colonoscopy and need not be removed unless symptomatic. In both of our patients pedunculated polyps were encountered. The submucosal nature of these polyps was not apparent and they were consequently excised. Removing a submucosal lesion probably increased the risk of perforation.

Neither the previously reported patient nor these two patients were very ill. In all three there were some signs of peritoneal irritation, but within a short time after initiation of broad-spectrum antibiotic therapy, two patients went on to uneventful recovery with complete resolution of all subcutaneous and retroperitoneal emphysema. It is quite probable that broad-spectrum antibiotic therapy alone would have been efficacious in case 2. In patients with gross tears and perforation due to colonoscopy, operative intervention will usually be required. We recommend that a patient in whom retroperitoneal emphysema develops following colonoscopy, with or without polypectomy, even in the presence of a small amount of intraperitoneal air, be managed conservatively. Treatment should consist of nothing by mouth, intravenous fluids and broad-spectrum antibiotics with close clinical observation. Such a conservative, nonoperative approach may be pursued unless clinical deterioration occurs.

Summary

Two cases in which retroperitoneal emphysema developed in addition to free intraperitoneal air after colonoscopic polypectomy are reported. In one case there was a benign clinical course and the patient was successfully managed nonoperatively. In the other patient, also with benign abdominal findings clinically, exploratory celiotomy was done to find and repair the site of perforation. The site of perforation was not found. Gross tears or perforation as a result of colonoscopic manipulation usually will require immediate surgical operation. Operative intervention for small perforations due to biopsy electrocautery should be reserved only for patients in whom there is no response to medical management within 48 to 72 hours.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

The Science and the Art

To the Editor: There is substantial basis for the editorial concern (Trends in the science and the art [Editorial]. 128:152-153, Feb 1978) with Food and Drug Administration Commissioner Donald Kennedy's desire to limit the marketing of drugs solely to those proven effective "by rigorous experiment"—a desire that is suspect because of its implications to other services and procedures. Your thoughts serve as a needed reminder of the Osler tradition, which blended the old art of medicine with developing scientific accomplishments. Such a blend, notably lacking in our younger medical generation, continues to be an indispensable prerequisite to a sound medical education and a sound subsequent practice.[1]

Although the cost factor appears on the surface as the initiating impetus or pretext, it merely acted as a catalyst for the overly scientific emphasis. Even before we became aware of the maelstrom of economic woes, many in medicine began to conduct themselves as if all of medicine had reached the precision and vigor of an exact science, immune to the obsolescence of its hypotheses. Moreover, particularly in the last decade, there were inroads on the professionalism of medicine. There appeared a deluge of economists who labeled medicine a trade or business and de-emphasized its predominant role, relegating its humaneness to the background or often cynically dismissing it. Not-for-profit hospitals were singled out as "obviously an industry,"[2] projecting an image of ailing human beings as industrial commodities. Even some of our organizational leaders[3] joined in such conceptualization, disregarding the distinguishing profit motive which is the mainspring of the commonplace variety of business. This, of course, is not to deny the need of a prudent and selective retrenchment in health care but it also recognizes the growing mischief of a lack of concern for the worth of human health and life.

There has been little recognition of the need in medical centers and political circles of safeguards against the prevailing idolatry of medical science. Such a need is evident—and the February editorial draws particular attention to it—in the pronouncements of our medical colleagues in government. Because of such idolatry, the practitioner has a tough assignment in trying to remain humane and to practice the art of medicine.

Medicine represents, as A.M. Ludwig so aptly phrased it, "a blend of empirical observations, scientific knowledge, unproved assumptions and folklore."[4] The current data are often ambiguous. There are no unequivocal answers to all medical diagnosis or treatment. It is not very comforting to note the vanishing of expressed doubt and uncertainty that had pervaded earlier medical practice which admittedly was much less knowledgeable.

It is reasonable to assume that the recognition of our limitations, and they are many, would spawn some long overdue modesty and humility —safeguards worth meditating on. Such modesty and humility "that good scientists should have engraved in their very souls,"[5] coupled with the cultivation of humanism, would be likely to have a contagious, sobering effect on the public's interpretation and expectations and, thereby, its presently overpowering and misconstrued urge to seek a remedy for mishaps in legal channels. Moreover, through the proper adoption of such

an approach, physicians become tempered by an awareness of the self-assurance of true reality, worthy of a mature physician.

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Trends in Obstetrics

To the Editor: My long-time friend and colleague, Peter Hughes, was in a foul mood the other morning. "I'm going to quit doing OB," he grumbled over his midmorning cup of coffee. "It just isn't fun anymore. It's becoming mechanized and dehumanized. Added to that, there is the ever present threat of malpractice that makes me uncomfortable."

"It used to be that the attending physician was the captain of the ship in the OB department," continued friend Peter. "But now our importance is diluted by the OB nurse who hooks our OB patient to the fetal monitor almost as soon as she walks through the door. And then she may proceed to invade the uterine cavity as she screws an electrode into the baby's scalp, or shoves up an intrauterine catheter. Just let the squiggles on the fetal monitor tape get a little erratic, and she begins to look at me cross-eyed for not rushing the patient in for a cesarean section. I've had it. I'm quitting."

Are not these typical of the comments we have been hearing lately from colleagues who are getting ready to throw in their accoucheur's sponge, or preparing to put away their axis-traction forceps, their DeLee fetus scopes? They say "Let those young fellows take over with their fetal monitors, their repeated amniocenteses, their cesarean sections done at the drop of a late deceleration."

Yet there are some of us who hate the thought of giving up OB. We know the sheer joy of bringing a new life into the world, of hearing that first cry, of seeing that exultant look of happiness on the new mother's face.

We do have our moments of doubt. At times we wonder, as we try so hard to exercise patient nonintervention we were taught was the essence of obstetrical art, whether those old fundamental teachings are really worth clinging to when, indeed, it seems that obstetric aggressiveness is the order of the day.

There was a time, for example, when delivering a baby by cesarean section was an admission of defeat—for the mother as well as the physician. A day when we strove to develop our skill with forceps, and when the ability to deliver a difficult breech was looked upon as a worthy accomplishment. In that day maternal morbidity and mortality was the prime consideration.

Now we are in a period of rapid change. Obstetrics is becoming less of an art and more of a science. The availability of fetal monitoring; oxytocin challenge tests; laboratory evaluations of serum estriols, bilirubin and palmitic acid, and L/S ratios suggests that mechanical devices and esoteric scientific data are threatening to replace good old-fashioned clinical judgment.

Moreover, the rights of the fetus are now being equated with those of the mother. Sophisticated (and expensive) neonatal intensive care units and the rapidly rising star of the neonatologist bear witness to that.

We are sorry that friend Peter, and others like him, are deserting the ranks. Now those of us who intend to stay in this happy business of bringing babies into the world must accept the increased responsibility of applying the new technologies judiciously and appropriately. After all, it's still the attending physician, not the nurse or the electronic machine, who must make the judgment call. To do this wisely and well we may have to unlearn some of the old obstetrical dictums, reevaluate some of our practices and stay abreast of new developments.

We need to urge senior staffers like Pete to stick around long enough to temper the boundless enthusiasm for medical gadgets and invasive obstetrics—at least until the final answers are in.

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President Lincoln's Illness

To the Editor: The diagnosis of Marfan syndrome for President Lincoln [Schwartz H: Abraham Lincoln and cardiac decompensation—A preliminary report. West J Med 128:174-177, Feb 1978] seems very doubtful to me.

Few Presidents had such extensive life examinations made as President Lincoln; because of his features he was sculpted more than any of the other Presidents, he was congenial and consenting to the artists, and they recorded even finite matters about the President. One woman sculptor, the precocious Miss Vinnie Ream, made several plaster bas reliefs and busts of Lincoln in 1864, and he sat for her numerous times; Congress commissioned her to do a full length Lincoln for the Capitol, paying her the unusual sum at the time of $10,000.00, much to the disgust and anguish of Mrs. Mary Lincoln, the President's widow. None of her observations confirmed or pointed to the eye or skeletal deformities.

The most famous sculptor of Lincoln was Leonard Wells Volk, who made a life mask of Lincoln in 1860. To save him a number of sittings, Volk took a plaster cast of his face, a painful process that Lincoln submitted to with characteristic good humor, although it made his eyes water and pulled out hairs when it was removed. Volk made his famous life-sized plaster statue for the Illinois State Capitol from the life mask, and a painting of Lincoln, and the famous casts of Lincoln's hands done in 1860 after the inauguration.

Lincoln was a practicing lawyer working on a major law case in Chicago at the time of the face cast, and no reference was made to the eye difficulties present in 50 percent of patients with Marfan syndrome. It is hard to conceive that the popular President had any eye problems that he could or would conceal. Indeed he often dwelled on his disabilities as in his talks with Attorney General Speed.

In no place can one find reference to bony deformities of the chest or bones. During one sitting Volk referred to his breast and brawny shoulders, and made Lincoln peel down his underwear so that he could show them as "nature presented them," which seemed great although large.

Most famous were the casts of Lincoln's hands made by Volk in 1860 in Springfield, Illinois. The right hand was swollen, probably from greeting well-wishers following his nomination two days earlier. Volk suggested that Lincoln grasp something while the cast was being taken, and the candidate left the parlor for the woodshed to saw off a piece of broom handle; when he returned he was trimming the piece with his pocket knife, stating that he wished to have it look nice. These are big, strong hands; not the hyperextendable weak hands seen in Marfan syndrome.

Except for his unusual height of 6′4″, there seem to be absolutely no eye or skeletal indications that Lincoln had Marfan syndrome.

I do believe that Lincoln had aortic insufficiency, as described by Dr. Schwartz. Contrary to Dr. Schwartz's feeling that Lincoln had no emotional distress while President, another Lincoln sculptor (Thomas Dow Jones) noted that Lincoln became very melancholy as his first inauguration drew near, transforming his face to an iron mask, which Lincoln said "looked like the critter."

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Registered Nurses and Long-Term Care

To the Editor: A major deficiency in the provision of health care today is the failure of physicians to fulfill their responsibilities toward chronically ill patients in nursing homes. This group constitutes one of the largest and most costly segments of the health care system in this country. Attempts to involve physicians more effectively have been almost universally unsuccessful. A fundamental change is needed.

It is proposed that the function of registered nurses (RN) in skilled nursing facilities (SNF) be altered radically, and the status of physicians in SNF be changed completely. In substance, it is suggested that primary responsibility for *continuing* direct patient care be placed on the registered nurse in charge of the SNF, retaining a physician solely as consultant to the RN when requested.

It is obvious that the responsibility of the physician toward chronically ill patients should not differ from his or her responsibility to acutely ill patients. It is well documented that such responsibility has failed in nursing homes, with few notable exceptions. Increasing regulations have been imposed on long-term care facilities over the past decade or more to cope with difficulties stemming from failure of physician involvement as presently operative. The most recent symptomatic remedy has been the requirement that a medical director be retained in each facility certified for the Medicare program.

The long-term care facility, as exemplified by the SNF, is an anomaly presently patterned after the prototype of the acute general-care hospital. In practice, there is little resemblance between the two at the operating level.

It is suggested that the acute hospital model for SNF's be abandoned, and that nursing homes be recognized for what they are in practice. They are institutions in which nursing care is provided by nursing personnel to patients with relatively stable illnesses over long periods of time. Physicians should be relieved of *continuing* responsibility in SNF's except as professional consultants to the registered nurses as needed.

As proposed, a physician will refer his patient to the SNF, accompanied by a written history, report of physical examination, listing of diagnoses, estimation of rehabilitation potential and orders for continuing medical treatment. The physician will be required to consult with the registered nurse in person at the time of admission for appropriate interchange of information. He then will be relieved of *continuing* responsibility except as the medical consultant to the RN. The RN will be expected to formulate health care plans for the patient and to implement them professionally. When and if there is need for change in therapy, as judged by the RN, the physician will be expected to respond as consultant. He may change the orders, or he may arrange for transfer of the patient to an acute general hospital if necessary. The RN will be charged with exercising good clinical judgment in carrying out this new responsibility.

This radical departure from current practice could become operative only after exhaustive study of its legality, feasibility, practicability and morality. It would require legislative changes for its implementation as well as far-reaching realignment of physicians' attitudes. It could signal the start of a new era in the larger field of health care.

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More on Libraries

TO THE EDITOR: In the February 1978 issue, Dr. Frank and Ms. Widmeyer responded to our letter "Concerning Libraries in Small Hospitals" published in the December 1977 issue. They describe their approach as a satisfactory low cost alternative to the use of a consulting medical librarian. However, they neglect to mention their use of the reference services of the Medical Librarian of Vallejo General Hospital.

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* * *

TO THE EDITOR: To add perhaps a final note to the Vallejo library discussion[1,2] (December 1977 and February 1978), I will recount my experience. I am a pediatrician in private practice who is on the courtesy staff of the Kaiser hospital in Vallejo. This facility has a large, well-organized and beautifully maintained library which is about half a mile from the previous two Vallejo physicians' bases of operation. I have been able to use that library for the past 20 years without problem.

The letter writers have offered solutions for community hospitals without access to other facilities, not mentioning what is already available—but why simplify?

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Refer to: Rosinski EF: The Central San Joaquin Valley Area Health Education Center (Medical Education). West J Med 128:355-359, Apr 1978

The Central San Joaquin Valley Area Health Education Center

EDWIN F. ROSINSKI, EdD, *San Francisco*

With federal financial support, an area health education center was established in the central San Joaquin Valley of California. The center is a cooperative health sciences education and health care program organized by the University of California and some of the educational and health care institutions of the valley. The center's goals include providing and improving primary health care education, and improving the distribution of health personnel. These goals are achieved through the cooperative development of a number of independent and interdependent activities. An extensive evaluation of the Area Health Education Center has shown that it is a highly effective program.

THE CARNEGIE COMMISSION ON HIGHER EDUCATION in its *Report on Higher Education and the Nation's Health* proposed the development of area health education centers (AHEC) as a means of developing health manpower in geographic areas without a university medical center. In making the proposal, the Carnegie Commission defined the role of an AHEC:

> . . . centers would be affiliated with the nearest university health science center, and would perform somewhat the same functions recommended for university health sciences centers except that the education of MD and DDS candidates would be restricted to a limited amount of clinical education on a rotational basis, and research programs would be largely restricted to the evaluation of local experiments in health care delivery systems.[1]

As proposed by the Commission, the AHEC's would essentially be extensions or satellites of university health science centers. The AHEC's would be visited regularly by university faculty who would give lectures and seminars, attend clinics, make ward rounds and the like. Educational programs would be developed by the participating institutions in collaboration with the university faculty. As the AHEC's developed, they in turn would provide assistance to other community institutions and health care facilities.

The AHEC concept had almost instant approval from most quarters of health sciences education. The federal government endorsed the AHEC concept because past experience indicated that university health centers could not respond, by themselves, to such pressing issues as geographic and specialty maldistribution of health personnel. It was believed that a consortium of institutions—secondary schools, community colleges, state colleges, universities, community hospitals and clinics, governmental and private agencies, voluntary health agencies, health professions organiza-

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ABBREVIATIONS USED IN TEXT

AHEC = area health education center
CSJV = central San Joaquin Valley
UCLA = University of California, Los Angeles
UCSF = University of California, San Francisco
VMC = Valley Medical Center

tions and others—working together, each contributing a unique resource in the development of health personnel programs, was an approach that had merit and should be tested.

Legislation to support AHEC's was developed and the Comprehensive Health Manpower Training Act of 1971 (Public Law 92-157) enacted by Congress made them a reality. Section 774A of that law suggested that a number of goals be established for federally supported AHEC's. They included, among others, the following: identifying the need for health personnel; providing educational programs for medical students, residents and allied health personnel; providing continuing education programs for health personnel; developing resources in order to attract health personnel to medically underserved areas; coordinating health personnel training programs, and developing new health careers.

To encourage the development of AHEC's, the federal government invited university health sciences centers to submit proposals on how they might initiate such programs in their areas. The federal invitations were in the form of a Request for Proposal (RFP) for contracts that would be critically reviewed and would be competitive. Funds were limited, consequently the initial number of AHEC's also would be limited.

The schools of medicine of the University of California, San Francisco (UCSF) and Los Angeles (UCLA), viewed the AHEC concept as one means by which they could extend their resources to a medically underserved area in California, while at the same time assisting the area in the development of its own health sciences education and health care resources. While many areas in California might qualify as being "medically underserved," it was agreed that the central San Joaquin Valley (CSJV) had the potential to continue the development of its health sciences education and health care programs when university participation in the development and operation of the AHEC came to an end.

The CSJV was an excellent place in which to locate and initiate an AHEC. For many years the community had a strong interest in beginning a medical education activity and superb leadership was provided by a number of outstanding persons in the community. The community leadership organized itself into the Central San Joaquin Valley Health Consortium and the consortium had as its primary goal fostering the development of health sciences education in the area. Furthermore, the community had developed the groundwork for a program such as the AHEC through its involvement in a number of activities related to the former Regional Medical Program, and from the efforts to establish a modified AHEC approach through funding by the Veterans Administration at the Fresno Veterans Administration Hospital. It was an appropriate time for a joint effort between the medical schools and the CSJV Health Consortium to launch a program that would expand and develop the valley's health sciences and health care resources.

The schools of medicine at UCSF and UCLA were fully aware that it would be presumptuous to initiate unilaterally an AHEC in a community almost 250 miles away. Since the schools had good relations with the health consortium it was relatively easy to get the concerned parties together to develop AHEC proposals. Finally, both UCLA and UCSF prepared proposals, but the government decided that the two proposals should be combined, and awarded the contract to UCSF. The deans of both medical schools then decided which campus would be responsible for what, and the Central San Joaquin Valley AHEC—one of 11 area health education centers approved and funded in the country—began operation. The San Francisco campus was designated the prime contractor, while UCLA contracted to carry out certain activities and fulfilled its contractual obligations.

For a project as large as the CSJV-AHEC, the administrative staff is remarkably small. The Project Director is the Associate Dean, Extended Programs in Medical Education at UCSF, and he has a full-time assistant who handles the day-to-day operation and supervises the staff, almost all of whom are located in Fresno. In addition, the position of Associate Director, UCLA, has been maintained to provide leadership for the UCLA activities. The Project Director has an advisory committee consisting of members of the AHEC community, and faculty members from UCLA and

UCSF. The advisory committee meets at regular intervals to discuss and consider policy and, once a year, to select its own chairperson.

Staff meetings, consisting primarily of the directors of each of the component programs, are held at irregular intervals. The purpose of the staff meetings is to keep everyone involved in the project informed about activities in each component program. Once a year the program directors submit their plans and budgets for the coming year to the Project Director and these plans are discussed at a staff meeting. The Project Director submits a budget to the Department of Health, Education, and Welfare where it is critically reviewed by the contract officer of the local Department of Health, Education, and Welfare Regional Office.

An unusual feature of the AHEC legislation was the requirement that every program be evaluated. With the federal government increasingly concerned with accountability, the legislation clearly stipulated that evaluation should be a major activity of each AHEC. Sensitive to the need for an impartial evaluation, the Project Director requested a number of persons to submit proposals to evaluate the program. One was selected and periodic reports are made to the Project Director on the progress of the entire project as well as the progress of each component program. A final report upon conclusion of the initial funding of the project essentially answered the question "Was it a success?"

The CSJV-AHEC began on October 1, 1972. The AHEC is a series of independent and interdependent individual programs all directed toward achieving one or more of the goals of the national AHEC program, which are the following: (1) To improve the specialty and geographic distribution, supply, quality, utilization, and efficiency of health personnel in the health delivery system. (2) To improve the regional development of educational responsibilities of health professions schools. (3) To effect change in the distribution of health personnel and the accessibility to quality health care in the AHEC area. The AHEC began with 13 programs and during year five, the last year of the initial funding of the project, there were 23 programs. During the course of the five years a number of programs were discontinued because they did not meet either the goals of the AHEC or the program objectives. Other programs were ended because they had met all of their objectives, while others were added which in the judgment of the Project Director and his advisory committee and the government were considered compatible with the overall goals of the AHEC. A brief description of some of the component programs should illustrate how the AHEC works.

One of the more specific objectives of the AHEC is to provide and to improve primary health care education in the valley. The family medicine residency program is affiliated with the Division of Community and Ambulatory Medicine of the School of Medicine, UCSF, and is one of several programs working toward achieving that objective. The family medicine residency program carried out the following activities in the valley: (1) developed an affiliation between the Valley Medical Center (VMC) and UCSF; (2) developed community medicine rotations in rural patient care facilities; (3) developed medical student elective clerkships at VMC; (4) used faculty from UCSF and other university health science centers as teaching consultants to the VMC, and (5) provided lectures and seminars at the VMC for medical students, residents and private practitioners.

Another program directed toward improving primary health care education is the video tapes program. Video tapes on primary medical care topics are developed by UCSF and made available to practitioners in the valley. The family medicine residency program and the video tapes programs are independent activities, but in many ways are interdependent because they are both directed toward providing and improving primary health care education.

As can be seen in the family medicine residency program, all of the UCSF efforts are directed toward assisting existing institutions in the valley by strengthening their capabilities to provide primary medical care. At the same time, it is appreciated that there are a number of resources in the valley that can be tapped for the education of medical students and residents—or in bureaucratic jargon, UCSF has sought to develop "linkages" between its campus and institutions in the valley.

A brief review of some of the other component programs should further illustrate how the entire project is geared toward achieving the three previously cited major goals of the national AHEC program. A drug information program provides drug information to health professionals on all aspects of drugs, drug therapy and drug toxicity. The biomedical library resources program had as its goal the improvement of biomedical resources and

information services. A health administrators program set out to upgrade the capabilities of rural health administrators. The pediatric nurse associate program first assessed whether there was a need for personnel of this type, and after determining that there was, began to develop an appropriate training program. The number of dental hygienists was increased through the development of the dental hygiene program at Fresno City College, and a program for training dental laboratory technicians was inaugurated at Merced Community College. A number of programs contained continuing education activities; these included medicine, dentistry, nursing and the allied health professions. One program had a rather specific objective and that was to promote the continuous improvement of services in the intensive care of patients. Perhaps while this program might not be considered primary medical care, it was felt that it was in keeping with the overall goals of the AHEC. All of the programs were directed either by UCLA or UCSF.

A considerable amount of effort went into the evaluation of the CSJV-AHEC. All of the results of the evaluation cannot be cited here because they are voluminous. Some specific results can be described, and these serve as tangible evidence of the success of this remarkable partnership between the University of California and the central San Joaquin Valley.

Because of the development of cooperative institutional arrangements, the number of health personnel trained in CSJV institutions has increased. In 1972, four programs were devoted to training approximately 41 health personnel. During the past four years of the AHEC, 12 programs trained approximately 550 health personnel. Of even greater significance is the fact that the University did not assume the responsibility for these programs, but that the AHEC served as the facilitator through which independent institutions in the valley could develop new programs and improve existing programs for the health professions. Except for some visiting consultants in medicine, there were no continuing education activities in the valley in 1972. During the five years of the AHEC, seven different types of programs trained approximately 33,230 health personnel. With federal financial support, the government's project and contract officers, the faculty of UCLA and UCSF, the institutions of higher education in the valley and the leadership of the community, the AHEC forged a relationship through which many of its health manpower goals have been achieved.

Another result of the AHEC is the expansion of continuing education opportunities for all health personnel practicing in the six counties making up the AHEC area. Programs for dentists, nurses and a variety of other health personnel have been offered. Interdisciplinary continuing education programs have been organized, and in medicine a number of rural hospitals have organized themselves into consortia in order to develop a more coordinated valley-based continuing education effort. As part of the evaluation of the continuing education effort a sample of the valley's physicians was surveyed and the results showed that among physicians there is a universal feeling that the AHEC enhanced the professional environment of the area. While it cannot be assessed, it appears safe to assume that this improved professional environment should result in improved health care.

Still another achievement, although not solely attributable to the AHEC, is the Medical Education Program developed by the School of Medicine, UCSF, and the Veterans Administration. The Medical Education Program is centered at the Fresno Veterans Administration Hospital and will be a branch of the UCSF School of Medicine. While creation of the Medical Education Program cannot be attributed exclusively to the AHEC, by granting the financial resources to the University for this program the Veterans Administration recognized that the AHEC had established the infrastructure upon which a medical education program could be developed.

The implications of the Medical Education Program for the valley are significant. In time the program will have the capability to expand into rural areas, and will be able to attract and to retain in the valley a variety of health personnel, thereby enhancing further the initial achievements of the AHEC. As the Medical Education Program expands, it will build on the existing AHEC programs, and this partnership will ultimately lead to the development of outstanding rural and urban health care resources.

It appears, however, that the greatest achievement of the AHEC is that it proved that a partnership between a university and a community is possible and desirable. The institutions that make up the AHEC all saw themselves as equal

partners and worked toward common goals. In working together, the expectations of the Carnegie Commission report that the resources of university health sciences centers could be used to assist underserved communities have been realized. It was also the hope of the Carnegie Commission that universities would share equally with all the appropriate institutions of a community in meeting the community's health manpower and health care needs, and this hope has also been attained in the CSJV-AHEC.

The success of the CSJV-AHEC can be attributed to a number of reasons. It was important that the University of California did not see itself as a monolith imposing itself on a community, but viewed itself as an institution with a responsibility and commitment to education and health care. The alert leadership of the CSJV community, on the other hand, recognized the potential of its own institutions in dealing with many of its health and health manpower problems, but appreciated the fact that outside resources were also needed. In harmony the University of California and the central San Joaquin Valley leadership worked diligently to develop the valley's resources in education and health care, thereby further enhancing the welfare of the valley as a community.

REFERENCE

1. Carnegie Commission on Higher Education: Higher Education and the Nation's Health: Policies for Medical and Dental Education. San Francisco, McGraw-Hill, 1970

Malnutrition in Patients With Malignant Lesions of the Head and Neck

MALNUTRITION frequently is at the root of complications occurring in patients with malignant lesions of the head and neck. And it has been proposed as the common denominator of the multiple complications which ultimately cause death in patients with major head and neck tumors. Dr. Paul Marx of Columbia University's Cancer Research Center recently commented that "Over half of all female cancer deaths and 30 percent of all male cancer deaths may be related to nutritional factors." Improved nutritional status is often a valuable complement to other therapeutic measures. For example, rats maintained on intravenous feedings could tolerate twice as much 5-fluorouracil as could control animals. Patients with head and neck malignancy are often considerably deficient nutritionally when first evaluated due to a combination of age, inadequate dietary intake, and associated disease such as alcoholism. Discomfort, ulceration, bleeding, infection, or difficulty with swallowing may already have produced a state of negative nitrogen balance.

—DONALD O. CASTELL, MD, *Bethesda*

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 10, No. 16, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Special Article

Refer to: Mills DH: Medical insurance feasibility study—A technical summary. West J Med 128:360-365, Apr 1978

Medical Insurance Feasibility Study

A Technical Summary

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There are risks of adverse outcomes to patients in the course of health care management. A study was undertaken to measure these outcomes in California for 1974. Secondary benefits of the study include new insights into the types and sources of disabilities caused by health care management and the development of new methods for carrying out generic adverse-outcome monitoring.

IN THE PAST FEW YEARS, California's professional liability insurance market has been in a crisis, with skyrocketing premium costs and limited availability of insurance. The effect of this crisis has notably increased the overall costs of health care in California.

In the public interest, the California Medical Association (CMA) and the California Hospital Association (CHA) felt it necessary to determine the feasibility of alternative systems of patient-disability compensation. What is needed, in contrast to the existing malpractice trials under tort law, is a system that will cost less to administer, and will stabilize compensation through scheduled, standardized benefits. In this way, patients who have disabilities as a result of health care management could be fairly compensated automatically, without having to prove fault. However, reasonable cost estimates for such alternative plans cannot be made without valid information concerning the type, frequency and severity of those disabilities for which compensation might be paid. Consequently, the Medical Insurance Feasibility Study* was undertaken.

It was the purpose of the study to obtain adequate information about patient disabilities resulting from health care management. In accomplishing this goal, the investigators did not intend to measure the quality of health care in California or to propose any particular compensation plan. However, the study developed classifications, nomenclature and evaluation techniques which, if utilized in a patient-compensation program, could lower administrative costs in contrast to the current courtroom system.

The author of this article was contractor, administrator and editor for the study. The principal investigators were the author; David S. Rubsamen, MD, LLB, of Berkeley; and John S. Boyden, Jr., MD, LLB, of Salt Lake City. With the help of CMA and CHA staffs, and with the assistance of outside experts providing medical auditing, data retrieval, and actuarial and biostatistical services, a random

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*Copies of the full report are available from Sutter Publications, Inc., 731 Market Street, San Francisco, CA 94103. Price per copy is $35, plus applicable California state sales tax for California residents. For CMA and CHA members, initial copy price is $15, plus applicable California state sales tax.

sample of 20,864 inhospital patient charts from 23 representative California hospitals was reviewed. All charts had discharge dates in 1974. This sample so closely matched a 759,223 sample from data supplied by the California Health Data Corporation for patient discharges in 1974 that the statistics developed in the study can be generalized to the universe of patients (3,011,000) admitted to short-term, acute care, nonfederal general hospitals in California in 1974.

The study was carried out in such a way as to eliminate the identification of all physicians and patients involved in the sample. The official report also eliminated the identification of participating hospitals.

Definitions

In order to accommodate a variety of compensation plans, the following definitions and classifications were created:

- *A potentially compensable event* (PCE) is a disability caused by health care management.
- A *disability* is a temporary or permanent impairment of physical or mental function (including disfigurement) or economic loss in the absence of such impairment.
- *Causation* is established when the disability is more probably than not attributable to health care management.
- *Health care management* includes both actions (commission) and inactions (omission) of any health care provider or attendant, whether or not the action or inaction constitutes legal fault.

While all PCE's are defined as disabilities caused by health care management, subdivisions were required since variations arise in their origin and proof:

- *Class 1—Adverse effects of treatment or procedures:* The occurrence of a new abnormal condition caused by a treatment or procedure, either diagnostic or therapeutic. This class involves the adverse effects of commission in health care management. Despite the reason for the treatment or procedure, the adverse effect itself is the measurable outcome (for example, postoperative wound infections, and drug reactions).
- *Class 2—Effects of incomplete diagnosis or treatment:* The occurrence of a discrepancy between the expected and demonstrated outcomes of an original abnormal condition for which health care management was sought or rendered. This class involves the failure to realize an expected outcome based upon the standard of optimal capacity (defined as the ultimate capability of a well-trained specialist, under optimal conditions, to accomplish an intended medical or surgical goal in the majority of instances). The optimal capacity standard represents the nearest approach in defining the limits of medical science. It is, in essence, the highest possible standard that might be applied to the process of medical care. This class includes acts of commission and omission in health care management (for example, delayed diagnosis and treatment of acute appendicitis leading to rupture of the appendix, requiring prolonged management).
- *Class 3—Effects of incomplete prevention or protection:* The occurrence of an abnormal condition caused by incomplete preventive or protective health care management. This class deals with abnormal conditions that are foreseeable and preventable under the standard of optimal capacity and are caused by omissions in health care management. The expected outcome for this class is always the prevention of the abnormal condition that constitutes the disability (for example, a disability arising from the fall of a sedated patient out of a hospital bed).

Three other classes were created but eliminated because they were not specifically measurable in this study. The omission of these classes, however, does not alter the significance of the final results. Most of the "excluded" PCE's were also measurable (and were measured) in classes 1, 2 and 3 if consequential disabilities had occurred.

Data Source

In the absence of an existing reporting system sufficiently reliable to measure PCE's, original patients' records were examined. Hospital charts, rather than physicians' office or clinic records, were chosen to ensure greater uniformity and statistical validity. To determine the frequency with which PCE's might be missed by reviewing inpatient charts only, 928 clinic records were examined in the sample hospitals; two PCE's (0.22 percent) were found. Both were minor, temporary disabilities. Neither would have been discovered by examining inpatient charts alone. While this exercise did not exclude the existence of PCE's not discoverable through review of inpatient charts, it did provide reason to believe that PCE's limited to outpatient causes and management are relatively few in number and minor in severity.

TABLE 1.—*The Seven-Grade Severity Scale Adopted for the Study*

Code	Description
3.0	*Minor temporary disability:* Not exceeding 30 days and not requiring surgery for its correction or treatment.
3.1	*Minor temporary disability:* Not exceeding 30 days but requiring surgery for its correction or treatment.
3.2	*Major temporary disability:* Lasting for more than 30 days but not longer than two years.
3.3	*Minor permanent partial disability:* Permanent conditions which are not functionally disabling in reference to everyday living and working (e.g., loss of spleen, loss of uterus).
3.4	*Major permanent partial disability:* Substantial damage, but not sufficient to cause complete loss of ability to perform most ordinary functions.
3.5	*Major permanent total disability:* Substantial damage, usually sufficient to alter life-style into a dependent position.
3.6	*Grave permanent total disability:* Complete dependency or short-term fatal prognosis.
3.7	*Death*

Threshold

Since a myriad of inconsequential events occur in health care management, a minimum threshold was required for carrying out this study. A disability (PCE) was counted only if it met one or more of the following conditions:

1. It *occurred during* the sample hospital stay and *lengthened* the patient's stay, or it *continued* after discharge from the hospital (for example, postoperative wound infection that did not heal substantially within the assigned length of stay).

2. It *necessitated* the sample hospital stay for observation or treatment (for example, admission for observation following a drug reaction in a physician's office).

3. It was *treated* during the sample hospital stay even though it occurred before admission and was not the reason for admission (for example, a patient is admitted for a fractured arm; during the time in hospital an abdominal, incisional hernia from a previous surgical procedure was repaired).

4. It was *present* during the sample hospital stay although it had occurred before admission, was not the reason for admission and was not treated during this admission, provided: (a) it had a severity rating of at least "major permanent partial disability," (b) it is not the type of disability that usually requires hospital admission for its management, (c) it arose from events subsequent to December 31, 1968—an arbitrary cutoff date—(for example, a child born in 1970, now blind from retrolental fibroplasia, was admitted to the sample hospital for the treatment of pneumonia. If this child's chart was part of the sample, the retrolental fibroplasia would constitute a PCE).

5. It was *caused* by an event *during* the sample hospital stay but did not become evident until readmission to hospital (for example, delayed small bowel obstruction due to adhesions following a hysterectomy done during the sample admission).

Conversely, a disability was not counted if it occurred during the sample hospital admission; it completely, or nearly completely, was resolved within the assigned length of stay; and it would probably not cause continuing disability following discharge.

Severity of Disability

A seven-grade severity scale, adopted from the Workers' Compensation program, was modified for the study (see Table 1). The modifications are similar to those utilized by the National Association of Insurance Commissioners in its 1975-1976 malpractice claims review.

Conduct of Study

After the creation of the preceding definitions and rules, participating hospitals were instructed on the selection of 1974 charts by department and quarter of the year. Because a large sample was required for statistical significance, a method of screening by trained data retrievers was established. With the assistance of medical audit experts the investigators created a set of 20 generic (nondisease and nonprocedure specific) screening criteria (discussed at length in the published report). They proved effective to eliminate 50 percent of the sample charts while missing less than 1 percent of the PCE's. The remaining 50 percent were then reviewed by one or more of the investigators to determine the presence or absence of PCE's. All positive findings were reviewed in group sessions to confirm the proof required for each PCE and to assure proper coding sequences. All final data were entered on an IBM System 32 computer.

PCE Results

In all, 970 PCE's were found to be attributable to 1974. This was 4.65 percent of the entire sam-

ple. Divided into classes, the values shown in Table 2 were produced.

Generally, PCE's occurred equally in both sexes; however, patients 65 and over had a significantly higher rate than those under 65 ($P<.05$). When PCE occurrences were correlated with the primary source of medical care payment, patients receiving health care at government expense had significantly higher rates than others ($P<.05$). Interestingly, this difference arose primarily in groups of patients under 65 (Table 3).

Distributing the PCE's on the severity scale shows 80 percent to have been temporary disabilities; 6.5 percent, minor permanent; 3.8 percent, major permanent, and 9.7 percent, death (Table 4).

Though the total risk of PCE's was less than 5 percent, the statistical expansion of occurrences from the sample to the statewide hospital population in 1974 produced sizable results: 140,000±8,700. Of these, 112,000 (80 percent) were temporary disabilities (86,000 lasted 30 days or less), and another 9,100 (6.5 percent) involved no functional handicaps for daily living and working. Only 5,300 (3.8 percent) were associated with lasting, functional disabilities. The final 13,600 (9.7 percent) PCE's resulted in death, but 25 percent (3,400) of these occurred in patients who probably would have died within one year from unrelated, underlying diseases or conditions (for example, a patient with terminal cancer who died prematurely from adverse effects of antineoplastic therapy).

Tort Liability

Part of the study was devoted to determining which PCE's would probably result in verdicts in favor of patients (or heirs) if malpractice lawsuits had been filed. In arriving at this decision, the investigators took many factors into account, such as the type and severity of the PCE, the circumstances by which it occurred and was managed and the state of the medical records.

Only a fraction of 1 percent (0.79 percent; $n=20,864$) of sample charts disclosed evidence indicating the probability of liability for incurred PCE's. Expanded to the statewide hospital population in 1974, this small rate still produced 23,800 ±3,600 liability PCE's, representing 17 percent of all PCE's. However, only 2,600 involved substantial, permanent disabilities. Another 5,800 resulted in death, but this figure includes 800 patients who probably would have died within one year from unrelated, underlying diseases or conditions.

Since most patients who file lawsuits for medically caused disabilities do so without real knowledge about the presence or absence of legal fault

TABLE 2.—*PCE Incidence Rates for 1974 (n=20,864)*

Class	*PCE's**	*Percent of Total*	*Rates and Ranges†*
1	796	82	3.81±.26%
2	144	15	0.69±.11%
3	30	3	0.15±.05%
Total	970	100	4.65±.29%

*All reported occurrences have been rounded to the nearest integer. Fractional occurrences had been produced by reconstituting a 0.75 sampling of charts of patients 65 years of age and older. All incidence rates and ranges were calculated on occurrences to the 4th decimal.

†All estimates of ranges are based on a probability of .95.

TABLE 4.—*PCE's by Severity (n=970)*

Severity Code	*PCE's: Percent of Total*
3.0	35.7
3.1	25.7
3.2	18.6
3.3	6.5
3.4	2.2
3.5	1.0
3.6	0.6
3.7	9.7
	100.0

TABLE 3.—*PCE Rates by Age and Health Care Payment Source**

	All Sources		*Government†*		*Nongovernment‡*	
Age	*n*	*Rate and Range*	*n*	*Rate and Range*	*n*	*Rate and Range*
65 and over	3,826	7.22±0.82%	3,483	7.32±0.87%	181	6.60±3.62%
Under 65	17,038	4.07±0.30%	3,566	5.16±0.73%	10,589	3.77±0.36%
All ages	20,864	4.65±0.29%	7,049	6.23±0.56%	10,770	3.83±0.36%

*The division into governmental and nongovernmental sources was based on 85 percent of sample. The payment source could not be determined in the remainder.

†Medicare, Crippled Children's Service, Medicaid (Medi-Cal), Welfare.

‡Private insurance, prepay/HMO, self-pay.

TABLE 5.—*Proportion of Liability PCE's and All PCE's by Severity*

Severity	*All PCE's as Percent of Total (n=970)*	*Liability PCE's as Percent of Total (n=165)*	*Liability PCE's as a Percent of all PCE's in Each Category*
Temporary (codes 3.0-3.2)	80.0	55.8	11.9
Minor permanent (code 3.3)	6.5	9.1	23.8
Major permanent (codes 3.4-3.6)	3.8	10.9	48.6
Death (code 3.7)	9.7	24.2	42.6
	100.0	100.0	17.0

TABLE 6.—*Relative Occurrence of Causal Factors Leading to PCE's*

Percent of Total	*Causative Event*
66.1	Specific procedures
18.8	Drugs and biologics
4.1	Medical devices
2.7	Nondiagnosis
2.6	General medical management
2.2	Misdiagnosis
2.0	Anesthetic management
1.6	Nursing management
100.1	

TABLE 7.—*Location of Causal Events in Sample Hospitals Leading to PCE's*

Percent of Total	*Location*
71.8	Operating room
12.0	Patient's room
5.8	Radiology
4.6	Labor and delivery
2.6	Emergency room
0.7	Nursery
0.4	Critical care units
2.1	Unknown/other
100.0	

as the cause of their disabilities, they have, on an average, only a 17 percent chance of success in their legal ventures. Just the few with more severe permanent disabilities and death have substantially better odds (44.3 percent) for successful legal outcomes.

Though PCE's generally occurred with greater frequency in older age groups, the proportion of liability PCE's was relatively constant among all age groups.

PCE's involving liability were, as a group, more severe than PCE's generally; therefore, the more severe the disability, the greater the risk of liability (Table 5).

Medical Causative Events

To gain preliminary insight into the types of health care management events that led to the PCE's measured in the study, PCE's of all classes were allocated to the primary causative categories listed in Table 6.

Based on the entire sample, a third of the causal events leading to PCE's occurred in the sample hospitals during the current admissions, a third occurred in the sample hospitals during previous admissions and a third occurred in some other hospital or medical office ("elsewhere"). Of all PCE's that arose from causal events in the sample hospitals, 72 percent were related to operating room events; only 2.6 percent were related to events in emergency rooms (see Table 7).

Other Observations

Postprocedural infections comprised the most frequent Class 1 PCE arising from specific procedures (29 percent). The procedure most frequently producing Class 1 PCE's was the total hysterectomy (6 percent). The largest single source of Class 2 PCE's was the management of fractures and dislocations (30 percent). Of causal events leading to Class 3 PCE's, 46 percent were related to nursing management.

Ten drugs were responsible for over 60 percent of all drug-caused PCE's. The leaders were estrogens and progestins, anticoagulants, adrenocorticoids and aspirin.

Patient-Caused Disabilities

Patients, themselves, were responsible for 12,600±2,700 disabilities discovered in the study to be attributable to 1974 (rate=0.42±.09 percent; n=20,864). Causative factors were either self-management of diseases or injuries, or failure to follow medical advice. Most such disabilities, however, were minor in severity. Drugs taken for health management purposes (not drug abuse)

accounted for 56 percent. Of the patient-caused disabilities arising from drugs, 49 percent were due to aspirin.

Conclusion

The purpose of the study was to accumulate data about the PCE universe to provide the opportunity to consider alternative compensation plans. This goal has been achieved. Secondary benefits have also accrued: (1) Medicine now has added insight into the types and sources of disabilities caused by health care management, whether or not due to legal fault; and (2) With modifications and appropriate guidance, hospital medical staffs now have the methodology to undertake generic adverse-outcome monitoring as a basis for self-assessment and prevention, when possible. Finally, the study should leave everyone with the realization that there are finite risks associated with health care management, most of which are unrelated to conduct characterized as legal fault. Society deserves the right to nourish great expectations from the advances in modern medicine, but *no one* should remain unaware that benefits and adverse risks are inseparable. When considering the circumstances under which these risks arise, their incidence rates are remarkably low. Only 4.65 percent of patients admitted to hospital were found to have incurred PCE's, and less than 1 percent of all patients admitted to hospital had PCE's due to legal fault.

Iridocyclitis and Papillitis Following Acute Febrile Respiratory Illness

A CERTAIN TYPE of anterior uveitis, particularly in young persons, appears to crop up about a week or ten days after an acute febrile respiratory illness. This, generally speaking, is an acute iridocyclitis and has been accompanied in a dismaying number of cases by involvement of the optic nerve head, an associated papillitis. That this disease is viral is only presumptive; it has not been proven. But the history of a febrile illness with respiratory symptoms a week or ten days before the onset of ocular symptoms has cropped up again and again in our series and may be important.

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Extracted from *Audio-Digest Ophthalmology*, Vol. 16, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

Refer to: Avina RL, Schneiderman LJ: Why patients choose homeopathy (Commentary). West J Med 128:366-369, Apr 1978

Why Patients Choose Homeopathy

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Interviews with 100 homeopathic patients in the San Francisco Bay Area show that for the most part the patients are young, white and well-educated, and have white-collar jobs; most had previously tried mainstream medical care and found it unsatisfactory. Among the reasons for their dissatisfaction were instances of negative side effects from medication, lack of nutritional or preventive medical counseling, and lack of health education. Experiences with conventional physicians were almost evenly divided: nearly half of the subjects reported poor experiences, slightly fewer reported good experiences. Three quarters of the patients suffered from chronic illness and about half considered their progress to be good under homeopathic care. The majority were simultaneously involved in other nontraditional health care activities.

ONE BENEFICIARY of the current popularity of the holistic health movement is homeopathy, a system of medicine based on doctrines propounded by Dr. Samuel Hahnemann more than 175 years ago.[1-3] Homeopathy does not subscribe to the germ theory or to much of modern physiology or pharmacology. Instead, homeopathic practice is based on a set of idiosyncratic principles such as: the Law of Cure or *Similia Similibus Curenter* (remedies are most efficacious which produce symptoms most similar to the disease), and the doctrines of Minimum Dose and Drug Potentisation (preparations are diluted even past their vanishing point and "dynamized" by vigorous shaking). Other principles which are somewhat less at odds with mainstream medicine include the Doctrine of Vital Force (the body's natural power of healing) and the Doctrine of Individualisation (the peculiarities of each person make his or her illness unique).

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From the perspective of modern medicine, homeopathy represents a vestige of medical history which once may well have served as a useful restraint on doctors when their interventions were more likely to cause harm than good; today it clearly lies outside the mainstream of medicine, although an occasional interest has been manifest in academic circles.[4-6] It is particularly remarkable that in these times when the latest medical marvels form the daily fare of newspapers, magazines, television and the movies, this vestige of history seems to have become revitalized. Are those who choose homeopathy less sophisticated, less well-educated than the general population? Are they from a socioeconomic group that is excluded from mainstream medicine? Is the appeal of homeopathy based on a reawakened interest in its principles? Or is its popularity rather a reaction against negative experiences with conventional medical care?

This study was undertaken not as a critique of homeopathic care, but rather as an inquiry into

its appeal. We hoped that information gathered from such a study might be of value to those within mainstream medicine who are trying to improve the effectiveness of their health care.

Methods

A total of 100 patients were interviewed between December 3, 1976, and January 5, 1977, using a structured, open-ended questionnaire at three different homeopathic practices in the San Francisco Bay Area. The physicians in charge were all licensed MD's who had taken up homeopathy after completing their conventional medical training. The interview locations were chosen to provide a cross section of patients seeking homeopathy. A total of 30 people were interviewed in a small suburban practice, 30 in a large incorporated suburban practice and 40 at a large urban center practice. To exclude selection bias by the interviewer, each patient was contacted sequentially in the lobby or waiting room as soon as a previous interview had been completed. The subjects had no prior knowledge of the questions to be asked and no contact with other interviewed persons before their own interview. Interviews lasted 10 to 15 minutes. Ten subjects refused to participate, five pleading time constraints, and one subject stopped in the middle of an interview because of "feeling uncomfortable." Three children 12 years and younger were interviewed through their parents. As a further observation, timed observations were made on 45 patients in the different clinics to determine the physician-patient contact time for first visits and repeat visits.

Patients were asked first to provide basic demographic data such as age, sex, marital status, family size, occupation, race and level of education. They were then queried about their reasons for seeking homeopathic care. Questions covered such aspects as what the nature of their problem was, what led them to seek the particular clinic they were attending, what their past experiences with their illnesses and doctors had been, what goals they were seeking, whether the principles of the homeopathic clinic were important in their choice, what medical problems would lead them to recommend homeopathy or mainstream medicine, and what other forms of health care they were getting.

TABLE 1.—*Selected Demographic Characteristics of Homeopathic Patients*

	Homeopathic Patients	*Comparison Population*
Percent white	96	89[7]
Percent under 45 years of age	75	60[7]
Percent female	66	61[7]
Average number of children in family	1.5	1.2[8]
Average years of education	14.2	12.3[8]

Results

Data from the three homeopathic settings were tabulated separately and then tested for homogeneity. Except where stated below there were no statistically significant differences in the data obtained from the three sources. The results presented therefore are pooled from all three settings.

Demographic Data

Table 1 illustrates the demographic characteristics of the study population compared with similar data obtained from other sources.

As a group the 100 homeopathic patients were young, single and white, and had a rather high educational level. A majority (57 percent) pursued white-collar occupations, 16 percent had blue-collar jobs, 16 percent were housewives and 11 percent were students. Of interest was the finding that a substantial percentage (11 percent) were themselves health care providers, including one MD, three RN's, three psychologists and four alternative form healers.

Medical Illness Data

Most visits (89 percent) were for symptomatic problems involving various organ systems. Well-care examination constituted 11 percent. In comparison, data from the National Ambulatory Medical Care Survey of 1973 show that 63 percent of visits were for symptomatic problems and 6 percent for well-care. (The remainder, 31 percent, fell into other categories.[7])

Most of the patients in this study suffered from chronic illness, 74 percent seeking care for conditions of longer than one year's duration and 34 percent for conditions that had lasted longer than five years. As an example, 15 of 18 patients with respiratory problems had chronic asthma.

Medical Care Data

Most (88 percent) of the homeopathic patients had previously consulted one or more conventional physicians for their condition, while 15

percent were seeing such physicians concurrently. In the urban center practice, which had been in existence for ten years, 45 percent of the interviewed patients had been obtaining homeopathic care for longer than a year and 20 percent for longer than five years. In the large suburban practice (in operation four years) and the small suburban practice (one year), more than 90 percent of the patients had just begun to seek homeopathic care within the year.

The homeopathic physicians used homeopathic remedies alone in 63 percent of the patients, and in combination with conventional medication in 11 percent. In 8 percent of the patients only conventional medicines were being used and in 18 percent no medications whatsoever.

About half (47 percent) of the patients reported good progress with their illness, 22 percent poor progress and the remaining 31 percent had no opinion or felt it was too early to tell—of the last group, 3 percent were making their first visit.

Many (77 percent) of the patients were involved in some other form of nontraditional health care, most commonly chiropractic treatment, but also acupuncture, yoga, therapeutic massage, hypnotherapy, primalism, applied kinesiology, osteopathy, polarity, shiatsu massage and rolfing.

Homeopathic physicians spent an average of one hour with new patients and 20 minutes for return visits. In contrast, the National Ambulatory Medical Care Survey of 1973 showed that in 75 percent of visits, physicians spent 15 minutes or less with their patients.[7]

Reasons for Seeking Homeopathy

Most subjects provided more than one explanation for seeking homeopathic care, some positively directed towards their expectations, others obviously in reaction to unhappy experiences with conventional medical care. Table 2 summarizes the responses related to previous experiences with conventional medical care in general. Table 3 summarizes responses related specifically to previous experiences with conventional physicians. Table 4 provides a summary of stated expectations of benefits to be gained from homeopathic care.

It is apparent that only a small number of patients (19 percent) claim that they were using homeopathy because it was consistent with belief or principle. A much larger number of patients (81 percent) described dissatisfaction with one or more aspects of conventional health care. Three patients stated that they chose to go to homeopaths when their conventional physicians had recommended surgical operation.

Several questions in the interview were designed to probe attitudes with regard to the use of health care providers for specific medical situations. Although 78 percent of the subjects said that they would use or recommend conventional physicians for emergencies, acute illnesses and orthopedic problems, 16 percent said they would not recommend such physicians for any reason. To the question "What would you do if you had low back pain?", 35 percent said they would treat themselves, 27 percent said they would seek homeopathic care, 24 percent would seek a chiropractor and 20 percent would choose other mo-

TABLE 2.—*Previous Experiences of 100 Homeopathic Patients With Conventional Medical Care*

Experiences Reported	*Percent of Sample Holding Attitude*
Dissatisfied with one or more aspects of conventional care	81
Belief that conventional treatment was failing	55
Dissatisfaction with medication side effects	55
Dissatisfaction resulting from lack of preventive medicine and nutritional orientation	21
Dissatisfaction resulting from lack of health care education	20

N = 100

TABLE 3.—*Previous Experiences of 100 Homeopathic Patients With Conventional Physicians*

Experiences Reported	*Percent of Sample Holding Attitude*
Poor experience with conventional physician	45
Good experience with conventional physician	40
Mixed experience with conventional physician	15

N = 100

TABLE 4.—*Reasons for Seeking Homeopathic Treatment*

Reason Reported	*Percent of Sample Reporting*
Seeking relief of problem without traditional medication	83
Seeking improved health education	33
Seeking improved health maintenance and disease prevention	21
Seeking improved dietary consultation	19
Treatment consistent with personal principles and beliefs	19

N = 100

dalities such as physical therapy, massage or rolfing. Only four of the 100 interviewed subjects would choose conventional physicians to treat the disorder.

Discussion

In an era when medical science has shown unprecedented diagnostic and therapeutic virtuosity, the popularity of an antique and mystical approach to health care such as homeopathy must seem puzzling. The phenomenon, however, seems to reflect a rising "disenchantment with modern science and a return to occultism."[9] At its center this movement focuses holistically on the person and reflects contemporary attitudes of psychology, sociology and politics. At its fringes, however, are a great array of alternative health care practices that derive from old, often exotic and apocryphal sources of authority which in general reject contemporary science and empiricism.

The patients seeking homeopathic care in this study certainly are not ignorant, unsophisticated or underprivileged, nor are they excluded from access to conventional medical care. Rather they seem to be "dissatisfied customers" who seek homeopathy in large part because of negative perceptions of and experiences with mainstream medicine. Most of these patients offer substantial challenges to medical care in that they have chronic problems lasting a year or longer. As could be expected these patients were not "cured" by their physicians. Nor were their physicians apparently able to satisfy them through continuing medical or emotional support, factors which ultimately diminished their effectiveness as health care providers. Whether homeopathy will do any better is uncertain, although this would be worth exploring—chiropractors, for example, have been found to be at least as effective as conventional physicians in treating low back pain.[10]

Although most of these patients were also involved in other nontraditional health care activities, it is possible that these providers—like homeopathic physicians—are not appealing to exotic desires, but rather to the contemporary, and by now conventional, wishes of patients to learn more about nutrition, prevention and self-care. Physicians trained in mainstream medical schools likely will fault much of the instruction given such patients, but so far they seem to have provided little alternative.

A further examination of those factors, not perceived or expressed by patients, shows that homeopathic physicians spend more time with their patients than conventional physicians. Homeopathic physicians devote meticulous attention to each symptom, whatever the origin. Indeed an important element in the therapeutic relationships seems to be an agreement on the uniqueness of each person's symptoms. In contrast, conventional physicians seek to fit symptoms into common diagnostic patterns. Furthermore, in a large number of these patients, conventional physicians would tend to look for psychological explanations for both the symptoms and the benefits gained. Homeopathic physicians, however, rarely make psychiatric diagnosis as such, seeing such disorders as but a part of the "constitutional complex." This would appear to be very acceptable to these patients, only a small percentage of whom perceived their illness as being emotional in origin. It may well be that the patients prefer the homeopathic approach which avoids stigmatizing labels, and this as much as anything may account for much of homeopathy's appeal.

Finally, both patients and practitioners in the homeopathic offices showed some degree of flexibility—indeed shared responsibility—in application of principles. Eleven percent of the patients made use of both homeopathic and conventional medications. Indeed, homeopathic physicians tended to involve the patients in the choice of therapy, usually employing homeopathic methods first, then in the event that such treatment failed, instituting conventional therapy.

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Refer to: Dewar CR, Shapiro SR, Merten DF: Tracheoesophageal fistula and associated malformations (Medical Information). West J Med 128:370-371, Apr 1978

Medical Information

Tracheoesophageal Fistula and Associated Malformations

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THE ASSOCIATION between an imperforate anus and genitourinary anomalies in infants is well known to urologists and pediatric surgeons.[1] More recently, a broader group of congenital defects has been shown to occur in a higher than random association. Say and Gerald[2] described the association among imperforate anus, vertebral anomalies and polydactyly. Quan and Smith[3] noted that tracheoesophageal fistulae, radial dysplasia and renal defects also tended to occur in these infants and they coined the term VATER association (vertebral defects, anal atresia, tracheoesophageal fistula [TEF], radial and renal dysplasia). Cardiac anomalies were subsequently noted to occur with a higher than expected incidence in these patients.[4] When three or more defects coexist, this group of defects is commonly known as the VATER association.[5]

The entity of TEF is a surgical emergency in the newborn and constitutes the most critical clinical consideration in most patients with the VATER association. TEF actually represents five anatomic entities of which esophageal atresia with distal segment fistula is the most common.[6] With early recognition, intensive care neonatal nursing and aggressive surgical management, survival has increased dramatically over the past three decades. In a review of 120 cases, German and co-workers[7] noted that mortality was directly related to birth weight and the presence of associated anomalies.

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Patients and Results

The records of 21 infants with TEF seen at the University of California, Davis-Sacramento Medical Center Affiliated Hospitals between 1970 and 1976 were reviewed. Sex incidence was equal. The results of therapy compare favorably with other series.[7] Two children have died (10 percent). Twelve are doing well after definitive surgical repair (57 percent). One child is well with a feeding gastrostomy at the age of 3 months. In two, periodic esophageal dilatation is required. One child experiences recurrent bronchitis and three have been lost to follow-up. Of these infants, 81 percent had one or more additional features of the VATER association (Table 1). Table 2 is a summary of these additional findings. Figure 1 is an example of sacral dysgenesis and bilateral radial aplasia in an infant born with a TEF and a high imperforate anus.

Discussion

This study confirms that the defects of the VATER association occur together in a higher than random incidence. A defect in mesodermal development common to all involved organ systems could be the basis for this association.[3] The trachea is formed from the esophagus through invagination and upward growth of a mesodermal septum.[8] Interruption or malorientation of this process could lead to TEF. Similarly, descent of a mesodermal shelf divides the cloaca into the urogenital sinus and rectum and anus. Maldevelopment here would explain imperforate anus or, possibly, vesicorectal fistula. Formation of the radius, the vertebral bodies, and the kidneys are also dependent upon intricate migration of mesodermal tissues. As those processes are essentially complete by the 35th day, the proposed defect would have to manifest itself early in embryologic life.

Regardless of cause, increased survival and quality of life of these young patients demands a thorough search for associated anomalies. Fortunately, renal function in our series has been uniformly normal, but investigation has shown potentially significant renal lesions in a majority of cases where uroradiologic investigation was undertaken. (There were three normal excretory urograms in our cases.) The possibility of fistulae associated with imperforate anus and neurogenic bladder associated with sacral agenesis must be kept in mind when evaluating these infants. We recommend routine urologic investigation with

an intravenous pyelogram and voiding cystourethrogram in patients born with tracheoesophageal fistulae or other manifestations of the VATER association when clinical condition permits those studies to be done safely.

Summary

In recent years it has become apparent that a more than random association exists among varying combinations of congenital defects which include vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistulae, and radial and renal dysplasia. A review of 21 cases of tracheoesophageal fistulae has confirmed these associations. We recommend that urological studies be done in these children.

TABLE 1.—*Incidence of Associated Anomalies in 21 Children*

Tracheoesophageal fistula (TEF) alone	4/21
TEF plus one anomaly	7/21
TEF plus two anomalies	8/21
TEF plus three anomalies	2/21

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TABLE 2.—*Associated Defects in 21 Cases of Tracheoesophageal Fistula*

System	*Incidence* *Number*	*Percent*	*Types of Defects*
Vertebral anomalies	11/21	52	8 cases hemivertebra (e); 1 case each sacral dysgenesis, fusion C_5-C_6, and fusion 1st and 2nd ribs
Cardiac anomalies	6/21	29	2 cases isolated ASD; 1 case each of tetralogy of Fallot, isolated PDA, pulmonary branch artery stenosis; 1 case ASD, VSD and PDA with hypoplastic aortic arch
Radial dysplasia	5/21	24	2 cases radial aplasia; 2 cases thumb anomalies; 1 case arachnodactyly
Renal anomalies	4/21	19	2 cases crossed renal ectopia; 1 case horseshoe kidney; 1 case dysplastic kidney
Anal anomalies	3/21	14	2 cases high imperforate anus; 1 case anal stenosis
Additional defects	..	..	2 cases cleft lip/palate; 1 case each choanal atresia, malrotation of gut and trisomy-18 with abnormal facies

ASD = atrial septal defect PDA = patent ductus arteriosus VSD = ventricular septal defect

Figure 1.—An infant with multiple anomalies. Tracheoesophageal fistula and high imperforate anus were noted at birth: **Left,** Sacral dysgenesis; **Right,** Radial dysplasia.

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9:45 am	ATHLETIC COLLISION INJURIES OF THE KNEE AND SHOULDER ..... Edward J. Greenwald, MD
10:30 am	Break
10:45 am	THE FEMALE ATHLETE ..... James M. Glick, MD
11:15 am	PANEL DISCUSSION
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1:30 pm	THE IMMORTAL RUNNER ..... Jack H. Scaff, Jr., MD
2:15 pm	EXERCISE-INDUCED ASTHMA ..... I. Marshall Postman, MD
3:00 pm	Break
3:15 pm	HYPERPYREXIA, HEAT EXHAUSTION AND OTHER MEDICAL COMPLICATIONS OF EXERCISE .. Theodore B. Berndt, MD
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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

OFFICE GYNECOLOGY—Robert H. Glass, MD, Associate Professor in Residence, Department of Obstetrics and Gynecology, University of California, San Francisco. The Williams & Wilkins Company, 428 E. Preston St., Baltimore, MD (21202), 1976. 280 pages, $24.95.

Dr. Glass has produced an excellent textbook with the publication of *Office Gynecology*. A look at the contents is enough to assure the reader that most of the problems encountered in daily office practice have been identified. To present the individual subjects, Dr. Glass has assembled an outstanding group of authors who are well known and acclaimed for their expertise in the subject area.

Each chapter is presented in a concise and easily readable fashion. The emphasis is on the practical aspects of the problem and its management. In so doing, the content is less didactic and academic than the usual textbook but is complete enough for most practitioners. This does not detract from the reference, but, I believe, enhances its value to practitioners because the most important recent research advances are presented in an understandable fashion and integrated into a practical approach to the problem. For those who are interested in more detail, a representative bibliography is available for each chapter.

I would urge all who have gynecological patients in their offices to read this textbook. It is not a reference to be placed on a shelf and looked at occasionally, but a practical approach to everyday problems and their management which can be used daily by all physicians treating women.

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THE PATHOLOGY AND SURGERY OF THE VEINS OF THE LOWER LIMB—Second Edition—Harold Dodd, ChM(L'pool), FRCS (Eng), Emeritus Surgeon to St. Mary's Hospital(London) Group, Royal London Homeopathic Hospital, King George Hospital, Ilford and Royal Hospital, Richmond; and Frank B. Cockett, MS(Lond), FRCS(Eng), Surgeon to St. Thomas's Hospital, London. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1976. 323 pages, $39.50.

The second edition of *The Pathology and Surgery of the Veins of the Lower Limb* like the first edition is a classic in its field. The previous edition has served for 20 years as the comprehensive text dealing with venous disease. It has been popular both in Europe and in America.

The new edition is timely because of new developments in vascular disease which aid immeasurably in the diagnosis and management of venous abnormalities. New advances which have occurred in phlebography or venography, Doppler flow studies and radioisotope methods have been very helpful in detecting the incompetent perforating veins and have led to a better understanding of the causes of chronic venous insufficiency.

The techniques of venography and ultrasound, coupled with pulmonary angiography and lung scanning, have also led to a much better understanding of the frequency and nature of pulmonary embolism.

Emphasis is placed on the role played by incompetent ankle perforators, particularly the three primary internal perforating veins that account for most venous ulcerations and venous insufficiency. The point that venous drainage of the superficial tissues in the erect exercising leg is inward to the deep veins via the perforating or communicating veins is a point that many surgeons fail to appreciate even today. The failure to recognize the important role of the incompetent perforating veins and the causes of venous insufficiency and venous ulceration accounts in part for the poor results in the surgical management of venous ulceration.

The detailed descriptions of the pathophysiology of venous disturbances and the clear illustrations of surgical procedures and of the anatomy of the veins represent as lucid and informative descriptions as are available today. The section on history of venous disease is illuminating and interesting. The section on thromboembolism covers the new developments in both the detection and management of this disorder. The management of peripheral deep vein thrombosis and the control of thromboembolism are discussed, as well as the posthrombotic syndrome—the latter discussion containing many helpful measures needed to deal with a syndrome that can be very distressing.

This fine volume should be an important part of the library of any surgeon who deals with venous disease.

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EPIDEMIOLOGY AND COMMUNITY HEALTH IN WARM CLIMATE COUNTRIES—The Late Robert Cruickshank, CBE, MD, FRCP, FRCPE, DPH, FRSE, Hon LLD(Aberd), Formerly, Professor of Bacteriology, University of Edinburgh; Professor of Social and Preventive Medicine, University of the West Indies, Kingston; Kenneth L. Standard, MB, BS(Lond-UCWI), MD(Lond), FFCM, MPH, FRSH, FAPHA, Professor of Social and Preventive Medicine, University of the West Indies; Hugh B. L. Russell, MRCS, LRCP, MFCM, DTM&H, DPH, Senior Lecturer, Department of Community Medicine, University of Edinburgh; Formerly, WHO Regional Public Health Officer, Eastern Mediterranean; Regional Adviser on Community Development, Southeast Asia, and WHO Liaison Officer with the Economic Commission for Africa; Foreword by Professor E. K. Cruickshank, OBE, MD, FRCP, FACP(Hon), Dean of Postgraduate Medicine, University of Glasgow. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1976. 492 pages, $18.50 (paper), $32.00 (cloth).

Many of the major diseases of warm climate countries today are those prevalent in the western world more than 50 years ago. Their importance, severity and even manifestations differ when present in developing countries. This information needs dissemination by experts—those who have studied the diseases in the disadvantaged and developed societies. In this book the epidemiology and control of diseases in developing countries, and selected aspects of community health ranging from sanitation to training of health workers, are discussed by 28 authors, many internationally known in their fields. The results range from excellent to dreadful.

The introductory chapters are unsatisfactory, too simple for persons with any background in epidemiology, yet too diffuse for those unfamiliar with epidemiologic terms and methods. Organization is unusual. For example, chapters 4, 28 and 38 deal with different aspects of malnutrition. A study of cervical cancer in Jamaica is out of place in a book with all other chapters devoted to review articles which are descriptive of conditions in more than one area. The choice of material for inclusion or exclusion is also surprising. For example, an early chapter details computer analysis for health planning—

surely neither available nor an appropriate use of resources for most developing countries. There is, however, almost no mention of fluke or flatworm infections or of cancer other than cervical carcinoma occurring in Jamaica.

The 22 chapters about infectious diseases are the best and at the same time the most disappointing. Here the contrasts between developing and developed countries are most obvious and least exploited. Tuberculosis, a major cause of morbidity and mortality in all developing countries, is not defined epidemiologically, rendering cost-effective control improbable; the chapter contains no data, no references, and only a single page relevant to bacille Calmette Guérin (BCG) vaccination. The epidemiology of amebiasis is nearly ignored, the disease described in a manner (possibly) appropriate to a beginning course in clinical parasitology, and the material is unreferenced. In contrast, many other chapters are thoughtfully written and filled with documented nuggets about disease patterns common in developing countries but rarely discussed in the usual medical literature. Those I liked best were the chapters on measles and whooping cough (David Morley), leprosy (T. W. Meade) and poliomyelitis (I. Dömök).

Selective reading in this book would be rewarding. A second and improved edition, following the examples set by some of the authors, would be an exciting and needed addition to the medical literature.

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PAEDIATRIC HAEMATOLOGY—Michael L. N. Willoughby, MA, MD, MRC Path., Consultant Haematologist to the Royal Hospital for Sick Children and Queen Mother's Hospital, Glasgow. Churchill Livingstone—Medical Division of Longman Group Limited, Longman Inc., 19 West 44th Street, New York, NY (10036), 1977. 434 pages, $39.50.

Pediatric hematology is a relative latecomer to the specialties in medical science and practice. In this country it developed in the 1930's when a few pediatricians became interested in blood diseases and unusual hematologic reactions seen in infants and children and emphasized that these were not merely atypical forms of recognizable blood changes seen in adults but were characteristic of young developing persons or peculiar to this age group. Whole books of pediatric hematology did not begin to appear until the mid 1940's and 1950's. In England this development has been even slower. There, hematology has been a specialty of pathologists and clinical pathologists. Few of the latter limited their practice and interests to the pediatric age group so that pediatric hematology in most medical centers did not flourish as a well-recognized subspecialty. In contrast to the United States where we have at least half a dozen textbooks of pediatric hematology, there have been none in England.

This has now been remedied by the publication of this relatively concise book by Dr. Willoughby. It is well-written, quite readable and covers the special subjects that make pediatric hematology generally different from blood reactions and diseases in adults. Most of the discussions are brief and to the point so that practitioners may find the book helpful in making a diagnosis and prescribing the treatment in a hematologic disorder in an infant or child. For pursuing any subject in greater depth, a good collection of references is appended to each chapter.

The only criticism I would have is that the author has been too brief in his treatment of iron deficiency anemia, by all odds the most common anemia of infancy, early childhood and even of adolescence. This important cause for physical and possibly even mental retardation is not expounded in sufficient depth. Adolescent iron deprivation is barely referred to and its causes and correction deserve more discussion. Certainly its occurrence in Great Britain must be as frequent as in this country. By contrast, folate metabolism and deficiency is given about three times as much space as iron deficiency. In the United States it is rarely seen in infants and children, probably less than one hundredth as often.

In most respects, this is a very acceptable first of its kind in Great Britain and a worthy addition to the subject. It should be useful to American practitioners.

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* * *

CALCIUM, PHOSPHATE AND MAGNESIUM METABOLISM—Clinical Physiology and Diagnostic Procedures—Edited by B.E.C. Nordin, MD, FRCP, DSc, Director and Professor of Mineral Metabolism, University of Leeds; Honorary Consultant Physician to the General Infirmary, Leeds. Churchill Livingstone—Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 683 pages, $60.00.

This 653-page volume is an authoritative monograph by the staff of the Medical Research Council Mineral Metabolism Unit in Leeds, Yorkshire. The preface states that it is designed to be a companion to *Metabolic Bone and Stone Disease* published in 1973. Perusal of the very ample list of references indicates that the present volume was completed in 1974. (The ten references published in 1975 are either by the staff and presumably in press in 1974 or papers presented at meetings held in 1974.) To my knowledge it is the most complete compendium on the subject to that date. Particularly strong are the unusually lucid, sensible chapters on histology and microanatomy of bone by Jean Aaron and the historical accounts of rickets and of adaptation to low calcium intakes in light of recent knowledge of vitamin D activation. It is well written, illustrated, edited and printed.

I believe the authors were unfortunate in their timing. So much new crucial information has appeared in the last four or five years that would explain and shorten sections of this excellent compendium. It reminds me of Hoskins' five volume *Endocrinology and Metabolism* that came out just before the discovery of insulin. For example, in this volume, the heterogeneity of parathyroid hormone is discussed but there is no mention of the clarifying discovery by Silverman and Yalow in 1973 that all four of the presently recognized molecular species occur in the parathyroid gland itself. This important observation means that the large primordial molecules, including proparathyroid hormone and the 84 amino acid molecule are cleaved to C-terminal and N-terminal fragments in the parathyroid gland. It also means that ectopic parathyroid hormone secretion is characterized by the sole presence of the large molecules since the cleaving enzyme is in the parathyroid gland but not in cancers of other tissues.

Unfortunately, the important difference in half-life of the various molecular species, which explains the divergent reports on the suppressibility of parathyroid adenomas is also omitted. Similarly, the convincing study by Lindsay and co-workers (May 16, 1976) supplementing the earlier reports of Aitken and associates (which are included) was one of the most significant of the studies that convinced both the Endocrinology-Metabolism and Obstetrics & Gynecology Advisory Committees of the United States Food and Drug Administration that estrogens are effective in preventing postmenopausal bone loss.

These data, of course, appeared after the book was complete. In this regard, it is gratifying to see that Nordin has also come round to the view that estrogen deficit is important in the causation of postmenopausal osteoporosis and that estrogens are valuable in its prophylaxis and therapy. The role of estrogen in inhibiting collagen breakdown probably explains these results; it is not included in this volume. An important reference on the frequency of hip fractures by Cave and Nordin, referred to several times, turned out to be "privately printed" and therefore not readily available.

As noted, most omissions relate to the timing of the publication. One cannot fault the referencing of a volume with approximately 2,400 well-chosen references. It is an excellent source book for active workers in this field. I know of no comparable reference. It must, of course, be supplemented by subsequent reports which, I am sure, will be included in the next edition.

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* * *

INTERPRETATION OF BIOCHEMICAL MULTITEST PROFILES—An Analysis of 100 Important Conditions—Paul L. Wolf, MD, Professor of Pathology, Division of Clinical Pathology, University of California, San Diego, School of Medicine, La Jolla. Masson Publishing USA, Inc., 14 East 60th St., New York City (10022), 1977. 296 pages, price not listed.

Dr. Wolf is one of the most enthusiastic and experienced interpreters of laboratory results. His correlations have been popular pedagogical exercises attractive to medical students and physicians, alike. In this volume he has gathered 104 examples of SMA 12/60 and SMA 6/60 panels that display abnormalities readily correlated with a diagnosis and, at times, abnormalities that provide the important clues to a diagnosis. He relates case histories and provides pertinent references. The type is clear and the panels neatly reproduced.

It is unfortunate that the presentation is marred by careless writing, inattention to good organization and some poorly selected references. While the discussions would be acceptable as informal bedside chats, in the reading thereof direction and succinctness are lost. In explaining mechanisms that account for abnormal levels of constituents in serum, Dr. Wolf lapses into imprecision, teleology and circuitous explanation. A few examples include the analysis of the panel for a patient (number 26) with decreased potassium levels and bulky stools; a patient (38) with elevated cholesterol values and edema; and a patient (62) with increased alkaline phosphatase values, among others. The case of a febrile patient for whom the use of an anticoagulant in drawing the blood is the cause of the abnormal tracing is listed as a "febrile patient with decreased calcium and alkaline phosphatase" rather than as an example of artifactual results.

The information contained in the tracings is useful and should be helpful to clinicians who have limited experience with reading and interpreting panels. For medical students and those who wish to learn clinical physiological relationships, the text is not appropriate. With a reorganized and clearer text the volume would be valuable, indeed.

A set of slides is available for each portion of the book: panels, histories and interpretations. The slides of panels and histories would be good teaching aids for group discussion.

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CLINICAL RADIOBIOLOGY—W. Duncan, FRCPE, FRCR, Professor of Radiotherapy, University of Edinburgh; Honorary Consultant Radiotherapist, Royal Infirmary and Western General Hospital, Edinburgh; and A. H. W. Nias, MA, DM(Oxford), DMRT, Consultant Medical Radiation Biologist, Glasgow Institute of Radiotherapeutics and Oncology, Belvidere Hospital, Glasgow; Honorary Clinical Lecturer, University of Glasgow. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1977. 226 pages, $22.50.

This well-written text with excellent illustrations discusses the field of radiobiology in great detail. Chapters included discuss cell survival curves, early effects of radiotherapy on normal tissues, acute radiation syndromes, late genetic and somatic effects of radiation therapy and upcoming advances in radiotherapy.

One particular chapter discusses the clinical applications of radiobiology. This chapter describes the different effects of varying dose fractionation schedules on tumors and normal tissue. This is an important chapter because clinical research protocols in the United States call for varying dose fractionation schemes.

Another important chapter deals with upcoming developments in radiotherapy and describes the high linear energy transfer (LET) types of radiation which are now being used in clinical trials. This chapter describes the possible clinical benefit that may be gained by combining hyperthermia with radiotherapy. Also discussed is the use of chemotherapy—for example, alkylating agents, and radiosensitizing agents in conjunction with radiotherapy.

Clinical Radiobiology discusses the important principles of radiobiology as applied to radiation oncology. The text describes the field of radiobiology in detail. Furthermore, several new considerations in radiobiology (such as high LET radiation and combined chemotherapy and radiotherapy) are reviewed more extensively than in other similar texts. This book is recommended for radiotherapists, whether in practice or research, and for therapeutic radiology residents.

LARRY D. GREENFIELD, MD
Director, Nuclear Medicine Department
Radiotherapist, City of Hope
Duarte, California

* * *

RECENT ADVANCES IN OBSTETRICS AND GYNAECOLOGY—Number Twelve—Edited by Sir John Stallworthy, MA, Hon DSc (Leeds & Otago), FRCS, FRCOG, Hon FRCSI, Hon FCOG(SA), Hon FACS, Hon FACOG, Emeritus Nuffield Professor of Obstetrics and Gynaecology, University of Oxford; Consultant Obstetric Surgeon, Royal Prince Alfred Hospital, Sydney; Honorary Associate, National Maternity Hospital, Dublin; and Gordon Bourne, FRCS, FRCOG, Consultant in Charge, Department of Obstetrics and Gynaecology, St. Bartholomew's Hospital, London; Consultant Gynaecologist, Royal Masonic Hospital, London. Churchill Livingstone—Medical Division of Longman Group Limited, Longman Inc., 19 West 44th Street, New York, NY (10036), 1977. 368 pages, $27.50.

Recent Advances in Obstetrics and Gynaecology is an excellent review of 13 selected topics and should be of great interest to both obstetricians-gynecologists and to other practitioners of reproductive medicine. The chapters cover four areas of reproductive physiology (neuroendocrinology, intrauterine growth retardation, prostaglandins and placental function), five gynecologic topics (pediatric gynecology, colposcopy, laparoscopy, vulvar carcinoma and tubal reconstructive surgery) and four obstetric topics (ultrasound, conduction anesthesia, shock and coagulative disorders). While each subject is carefully reviewed, the chapter on ultrasound is especially complete and timely.

RUSSELL K. LAROS, JR., MD
Professor and Vice-Chairman
Dept. of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

in memoriam

Crahan, Marcus Esketh, Los Angeles. Died January 11, 1978 in Los Angeles of acute myocardial infarction, aged 77. Graduate of State University of New York Upstate Medical Center, Syracuse, 1925. Licensed in California in 1926. Dr. Crahan was a member of the Los Angeles County Medical Association.

Ferguson, Thomas A., Fullerton. Died January 19, 1978, aged 54. Graduate of the University of Louisville School of Medicine, 1948. Licensed in California in 1954. Dr. Ferguson was a member of the Orange County Medical Association.

Fung, George Dern, San Francisco. Died January 13, 1978, aged 58. Graduate of St. Louis University School of Medicine, 1944. Licensed in California in 1945. Dr. Fung was a member of the San Francisco Medical Society.

Green, John Winston, Vallejo. Died January 19, 1978 in Vallejo, aged 91. Graduate of Rush Medical College, Chicago, 1908. Licensed in California in 1921. Dr. Green was a member of the Solano County Medical Society.

Hanson, Wayne Pierre, Long Beach. Died January 21, 1978 in Long Beach of pulmonary embolism, aged 62. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1940. Licensed in California in 1941. Dr. Hanson was a member of the Los Angeles County Medical Association.

Hutton, Edward L., Oroville. Died January 25, 1978 in Oroville, aged 53. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1956. Licensed in California in 1957. MD degree from California College of Medicine, 1962. Dr. Hutton was a member of the Butte-Glenn Medical Society.

Ladd, Ervin E., Loma Linda. Died October 27, 1977, aged 69. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1948. Licensed in California in 1952. Dr. Ladd was a member of the San Bernardino County Medical Society.

Leake, Chauncey D., San Francisco. Died January 11, 1978 in San Francisco of heart disease, aged 81. Dr. Leake was an honorary member of the San Francisco Medical Society.

Loebl, Katherine Maria, Van Nuys. Died August 1, 1977 in Canoga Park of heart disease, aged 74. Graduate of Medizinische Fakultät der Universität, Wien, 1928. Licensed in California in 1942. Dr. Loebl was a member of the Los Angeles County Medical Association.

MacCracken, Frank Earle, Fresno. Died February 3, 1978 in Fresno, aged 94. Graduate of the American School of Osteopathy, Kirksville, Mo., 1913. Licensed in California in 1927. MD degree from California College of Medicine, 1962. Dr. MacCracken was a member of the Fresno-Madera Medical Society.

Marsey, Charles F., Glendora. Died January 3, 1978 in Glendora of cardiac arrest, aged 59. Graduate of Kansas City College of Osteopathy and Surgery, 1947. Licensed in California in 1962. MD degree from California College of Medicine, 1962. Dr. Marsey was a member of the Los Angeles County Medical Association.

McLaughlin, Richard F., sr., Burlingame. Died January 28, 1978, aged 74. Graduate of Creighton University School of Medicine, Omaha, 1930. Licensed in California in 1943. Dr. McLaughlin was a member of the San Mateo County Medical Society.

Montanus, John J., Santa Ana. Died January 12, 1978, aged 80. Graduate of Long Island College of Medicine, New York City, 1924. Licensed in California in 1937. Dr. Montanus was a retired member of the Orange County Medical Association.

Moore, Charles C., Martinez. Died January 17, 1978 in Seattle, aged 58. Graduate of the University of Southern California School of Medicine, Los Angeles, 1951. Licensed in California in 1951. Dr. Moore was a member of the Alameda-Contra Costa Medical Association.

Musser, Leo Pratt, Walnut Creek. Died January 10, 1978 in Walnut Creek of heart disease, aged 89. Graduate of the College of Physicians and Surgeons of Baltimore, 1913. Licensed in California in 1919. Dr. Musser was a retired member of the Alameda-Contra Costa Medical Association.

Petrilli, Alexander, San Francisco. Died June 11, 1977 of myocardial infarction, aged 72. Graduate of the University of Rochester School of Medicine and Dentistry, 1933. Licensed in California in 1937. Dr. Petrilli was a member of the San Francisco Medical Society.

Schwind, Justin V., Santa Barbara. Died May 17, 1977 of myocardial infarction, aged 64. Graduate of Loyola University School of Medicine, Chicago, 1940. Licensed in California in 1955. Dr. Schwind was a member of the Medical Society of Santa Barbara County.

Thomsen, Frederick H., Anaheim. Died July 8, 1977 of heart disease, aged 51. Graduate of Philadelphia College of Osteopathy, Philadelphia, 1951. Licensed in California in 1954. MD degree from California College of Medicine, 1962. Dr. Thomsen was a member of the Orange County Medical Association.

Touriel, Elie Louis, Los Angeles. Died October 6, 1977 in Los Angeles of cardiac arrest, aged 72. Graduate of St. Louis University School of Medicine, 1933. Licensed in California in 1933. Dr. Touriel was a member of the Los Angeles County Medical Association.

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CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

April 16-21—**California Society of Anesthesiologists—2nd Hawaii Seminar.** Hyatt Regency Hotel, Waikiki-Honolulu. Sunday-Friday. 20 hrs. Contact: CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 6-7—**American Society of Anesthesiologists Workshop.** St. Francis Hotel, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

June 1-4—**California Society of Anesthesiologists—Annual Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401.

September 8-9—**Update of Anesthetic Drugs and Monitoring.** STAN. Friday-Saturday.

CANCER

May 6—**Pediatric Oncology.** PMC. Saturday

May 10—**Carcinoma of the Cervix: Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $25.

June 19-23—**Head and Neck Oncology.** UCLA. Monday-Friday.

June 29-30—**Oncology Conference.** USC at Disneyland Hotel, Anaheim. Thursday-Friday.

June 30-July 1—**International Endocuriotherapy Symposium.** USC at Hotel Bonaventure, Los Angeles. Friday-Saturday. 22 hrs.

EMERGENCY MEDICINE

April 15-22—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $300.

May 8-12—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

May 8-13—**Topics in Emergency Medicine,** UCSF at Ralph K. Davies Med. Center, San Francisco. Monday-Saturday.

May 10-12—**Emergency Room Radiology.** See Radiology, May 10-12.

June 3-4—**Critical Care Monitoring.** UCLA at Airport Marina Hotel, Marina Del Rey. Saturday-Sunday.

June 10—**Plastic Surgery for Emergency Physicians.** UCI. Saturday.

June 26-30—**Trauma—Major and Minor.** USC. Monday-Friday.

July 24-28—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

August 7-11—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Islandia Hyatt House, San Diego. Monday-Friday. 40 hrs. $325.

September 11-15—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel, San Diego. Monday-Friday. 40 hrs. $325.

MEDICINE

April 15-16—**Basic Approaches to the Rheumatoid Condition.** DREW at Incline Village, Lake Tahoe. Saturday-Sunday.

April 15-22—**Chronic Obstructive Pulmonary Disease—From the Beginning to the End.** International Center for Postgraduate Medical Education at Kona Surf Hotel, Hawaii. One week. 25 hrs. Contact: Ms. Kym Westenberg, ICPME, 3969 Cuervo, Santa Barbara 93110. (805) 967-0497.

April 19-21—**Echocardiographic Solutions to Clinical Cardiovascular Problems.** American College of Cardiology and UCLA at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 19-22—**California Blood Bank System—26th Annual Meeting.** Hilton Hotel, Fresno. Wednesday-Saturday. Contact: CBBS Central Office, P.O. Box 1340, Long Beach 90801.

April 24-29—**American Academy of Neurology — Annual Meeting.** Bonaventure Hotel, Los Angeles. Monday-Saturday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

$35, members; $55, nonmembers. Contact: Mr. Stanley A. Nelson, Exec. Dir., AAN, 4015 W. 65th St., Suite 302, Minneapolis, MN 55435. (612) 920-3636.

April 27—**Rehabilitation Symposium.** American Heart Assn., Greater L.A. Affiliate, at Biltmore Hotel, Los Angeles. Thursday. 6 hrs. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

April 29—**Advances in Cardiology: A Practical Approach for the Primary Physician.** UCD at Royal Bay Inn, Vallejo. Saturday. 7 hrs. $55.

May 1—**Current Problems in Neuromuscular Disease.** PMC at Hyatt on Union Square, San Francisco. Monday. 6 hrs. $95.

May 4-5—**Current Concepts in Medicine: Stroke.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 13 hrs. $200.

May 4-7—**American Society of Internal Medicine — Annual Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. Contact: ASIM, 535 Central Tower Bldg., 703 Market St., San Francisco 94103. (415) 777-1000.

May 13—**Cardiology Update.** DREW at Bonaventure Hotel, Los Angeles. Saturday.

May 13—**Controversies in Internal Medicine—2nd Annual.** San Jose Hosp. and Health Center, Inc., at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $35. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 16—**Common Skin Problems Seen in Office Practice.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, 199 E. Webster St., Colusa 95932. (916) 458-5844.

May 19—**American Heart Association, California Affiliate—Physicians' Scientific Sessions.** Vacation Village, San Diego. Friday. Contact: Marilyn Probst, AHA, Calif. Affiliate, 805 Burlway Rd., Burlingame 94010. (415) 342-5522.

May 19—**The Child With Heart Disease: The Practitioner's Role.** See Pediatrics, May 19.

May 20—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

May 22-26—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 22-27—**Comprehensive Nephrology Review Course—3rd Biannual.** Cedars-Sinai Medical Center at Marriott Hotel, Los Angeles. Monday-Saturday. $400. Contact: Andrew J. Lewin, MD, Hypertension Research, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048.

May 29-June 2—**Advances in Internal Medicine.** UCSF. Monday-Friday.

May 31-June 2—**Advances in Child Neurology: Chronic Neurological Disorders in Childhood and Adolescence.** UCSF. Wednesday-Friday.

June 3—**Infectious Disease Symposium.** Kaiser Foundation Hospital, Sacramento, at Kaiser Center, Oakland. Saturday. 5 hrs. Contact: Onera Roberts, Education Office, Kaiser Foundation Hosp., 2025 Morse Ave., Sacramento 95825. (916) 486-5965.

June 10—**Advances in Cardiology: A Practical Approach for the Primary Physician.** UCD at Waystation, South Lake Tahoe. Saturday. 7 hrs. $55.

June 14—**Acute and Chronic Diarrhea.** LLU. Wednesday. 4 hrs. $25.

June 15-17—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 24—**Allergy for the Office Practice.** PMC Saturday.

June 29—**Renal Stones.** PMC. Thursday. 6 hrs. $85.

August 25-27—**Dermatomycology.** UCSF. Friday-Sunday.

OBSTETRICS AND GYNECOLOGY

May 10—**Carcinoma of the Cervix: Diagnosis and Treatment.** See Cancer, May 10.

May 19—**Introduction to Colposcopy and Evaluation of Early Cervical Neoplasia.** UCD at Woodlake Inn, Sacramento. Friday. 7¼ hrs. $45.

PEDIATRICS

May 1-5—**Pediatric Review.** USC. Monday-Friday.

May 6—**Pediatric Oncology.** See Cancer, May 6.

May 11-13—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 13-20—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 28 hrs. $300.

May 19—**The Child With Heart Disease: The Practitioner's Role.** UCD at Woodlake Inn, Sacramento. Friday. 6 hrs.

May 20-21—**Neuropediatrics.** UCLA. Saturday-Sunday. 11 hrs. $165.

May 27-29—**American Academy of Pediatrics, California Chapter I, District IX.** Hyatt House, Monterey. Saturday-Monday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

May 31-June 2—**Advances in Child Neurology: Chronic Neurological Disorders in Childhood and Adolescence.** See Medicine, May 31-June 2.

June 8-9—**Pediatric Allergy and Immunology.** USC. Thursday-Friday.

September 20-21—**Brennemann Memorial Lectures—35th Annual.** Los Angeles Pediatric Society at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Los Angeles Pediatric Society, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

April 15-16—**The Nature and Management of Stress.** UCLA and UC Extension, Santa Cruz, at Monterey Conference Center, Monterey. Saturday-Sunday. 12 hrs.

April 17-19—**Stress Reduction and Self-Management Techniques.** UCLA and UC Extension, Santa Cruz, at Ahwahnee Hotel, Yosemite. Monday-Wednesday. 14 hrs. $200.

May 19-21—**Treatment of Schizophrenia.** UCSF. Friday-Sunday.

June 2-3—**Psychosocial Care of the Dying Patient.** See Of Interest To All, June 2-3.

June 17-18—**Practical Applications of Biofeedback in the Health Sciences—5th Annual Seminar.** See Of Interest To All, June 17-18.

June 26-30—**Comparative Psychotherapies.** USC. Monday-Friday.

June 30-July 1—**Human Problems: Ordinary and Extraordinary —3rd Don D. Jackson Memorial Conference.** Mental Research Institute at Sir Francis Drake Hotel, San Francisco. Friday-Saturday. Contact: Peggy Smith, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

RADIOLOGY AND PATHOLOGY

April 21-22—**Seminar and Wet Tissue Workshop.** USC. Friday-Saturday.

May 4-5—**New Concepts in Medicine: Stroke.** See Medicine, May 4-5.

May 10-12—**Emergency Room Radiology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday. 15 hrs. $160.

May 13—**Radiology Symposium.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

June 3-4—**Leo Rigler Radiology Seminar.** UCLA. Saturday-Sunday.

June 18-23—**Pathology of the Lung.** UCSD. Sunday-Friday. 50 hrs. $400.

July 30-August 5—**Ultrasound and Computed Tomography.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Saturday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

September 7-9—**American Electroencephalographic Society—Annual Meeting.** Hyatt Regency, San Francisco. Thursday-Saturday. Contact: American EEG Society Executive Office, 38238 Glenn Ave., Willoughby, OH 44094. (216) 942-9267.

September 9—**Gastrointestinal Radiology.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Saturday. 7 hrs. $30. Contact: Shirley Gach, Education and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4241.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

April 15-22—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 18—**Orthopaedics—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

April 20-21—**Current Concepts of Macular Structure, Function and Disease—9th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute and UCLA at Century Plaza Hotel, Los Angeles. Thursday-Friday. $225. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

April 20-21—**Current Problems in Intensive Care: The Cardiac Surgical Patient.** UCSF at Fairmont Hotel, San Francisco. Thursday-Friday. 11 hrs. $125.

April 21-22—**Vitrectomy Microsurgery Workshop.** VA Hospital, San Francisco. Friday-Saturday. 15 hrs. $350.

April 28-29—**Vitrectomy Microsurgery Workshop.** See above, April 21-22.

April 29-May 6—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $275.

May 4-5—**New Concepts in Medicine: Stroke.** See Medicine, May 4-5.

May 6—**Flexible Bronchofibroscopy.** PMC. Saturday. 6 hrs. $300.

May 6—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 11-12—**Office Orthopedics.** USC. Thursday-Friday.

May 20-22—**Neurosurgery—8th Annual Course.** UCSF. Saturday-Monday.

May 28—**Surgical Management of the Traumatized Patient—3rd Annual Clarence E. Stafford Memorial Surgical Symposium and Lecture.** White Memorial Medical Center and LLU at Bonaventure Hotel, Los Angeles. Sunday. 8½ hrs. $75. Contact: Dir. of Cont. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Box 127, Los Angeles 90033. (213) 269-9131.

(Continued on Page 30)

Tablets
Percodan® Ⓒ II

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg. oxycodone terephthalate (WARNING: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

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DUPONT

CONSIDERATIONS FOR ORAL NARCOTIC ANALGESIC USE:

1. Determine need

What is causing pain? How is it perceived by you and your patient?

2. Prescribe a rapid-acting agent

Select a readily-absorbed oral agent that usually acts within 15 to 30 minutes.

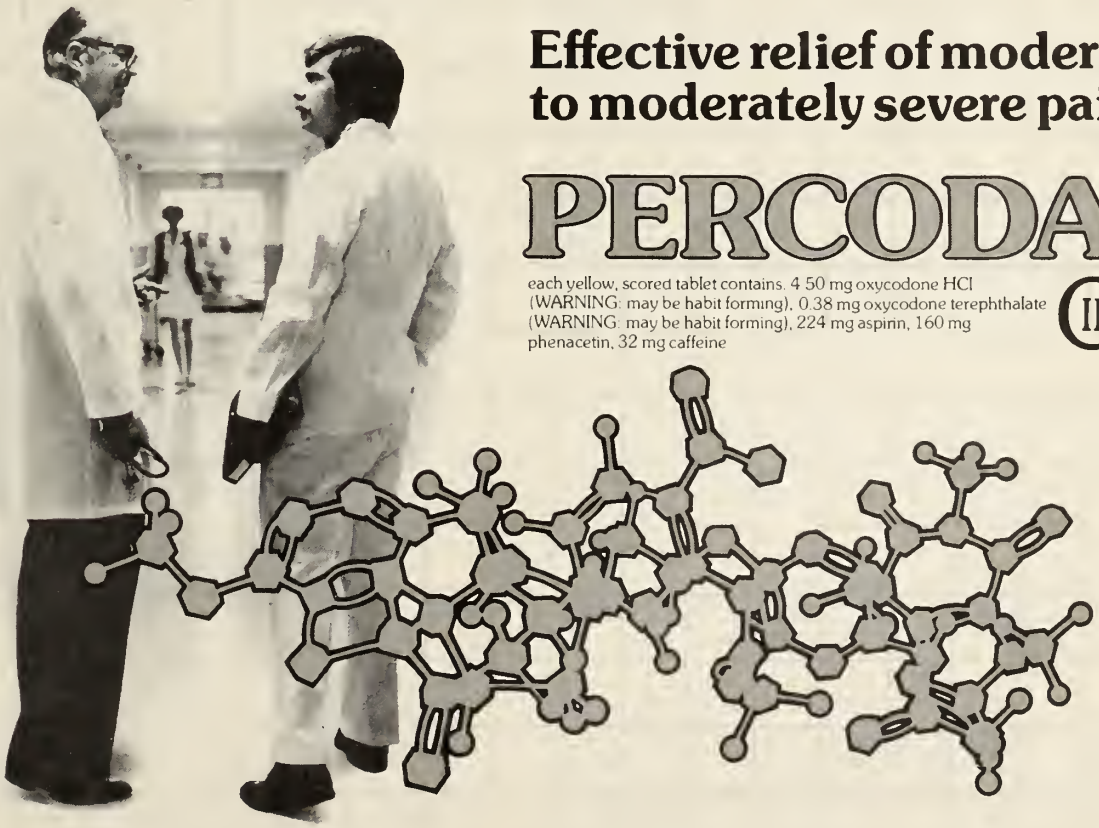
3. Minimize potential risk

Prescribe in limited quantities for selected patients.

Schedule II classification means no refills, no telephone Rx. Patients with persistent pain must return for your evaluation of analgesic needs.

4. Provide adequate analgesia with minimum doses

Consider PERCODAN® because patients rarely ask for increased dosage. PERCODAN® relief can last up to six hours–until time for next tablet.



Effective relief of moderate to moderately severe pain

Tablets

PERCODAN®

each yellow, scored tablet contains: 4.50 mg oxycodone HCl (WARNING: may be habit forming), 0.38 mg oxycodone terephthalate (WARNING: may be habit forming), 224 mg aspirin, 160 mg phenacetin, 32 mg caffeine

CII

PERCODAN® is a registered trademark of Endo Inc.

Please see facing page for Brief Summary of prescribing information.

(Continued from Page 28)

June 2-3—**Intraocular Lens Implantation Course.** Santa Monica Hospital. Friday-Saturday. $600. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

June 2-4—**Soft Tissue Surgery.** USC. Friday-Saturday.

June 5-16—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1200 for otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Dir., Temporal Bone Surgical Dissection Course, ERI, 256 S. Lake St., Los Angeles 90057.

June 9-10—**Ophthalmology Update VI.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 6 hrs. $225.

June 10—**Strabismus Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 11-15—**American Society of Colon and Rectal Surgeons—Annual Convention.** San Diego. Sunday-Thursday. Contact: Harriette Gibson, Admin. Sec., ASCRS, 615 Griswold, No. 516, Detroit, MI 48226. (313) 961-7880.

June 15-17—**Hip Course.** UCLA. Thursday-Saturday.

June 15-17—**Highlights of Ophthalmology.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday. 16 hrs. $195.

June 29—**Renal Stones.** See Medicine, June 29.

August 4-5—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

April 15-16—**The Nature and Management of Stress.** See Psychiatry, April 15-16.

April 16-22.—**Diving Medicine.** John A. Burns School of Medicine, Univ. of Hawaii, at King Kamehameha Hotel, Kailua-Kona, Hawaii. Sunday-Saturday. 25 hrs. $250. Contact: Hawaii Conference Services, P.O. Box 22670, Honolulu 96822. (808) 373-3045 or (808) 373-3745.

April 17-19—**Stress Reduction and Self-Management Techniques.** See Psychiatry, April 17-19.

April 18-19—**Hypertension.** USC. Tuesday-Wednesday.

April 20-21—**Health, Science and Society: Scientific Solutions and Human Problems.** UCSF at Sheraton-Palace, San Francisco. Thursday-Friday. $80.

April 22-23—**Practical Dermatology for the Primary Care Physician.** UCLA. Saturday-Sunday.

April 22-29—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 28-29—**San Joaquin Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday. Contact: Charlotte Newhart, CMA.

April 28-30, May 5-7—**Introduction to Sex Counseling Principles.** UCSF Human Sexuality Program. Two weekends. 50 hrs. $175 per person; $300 per couple. Contact: Human Sexuality Program, 350 Parnassus Ave., No. 700, San Francisco 94143. (415) 666-4787.

April 29-30—**Sports Medicine.** UCLA. Saturday-Sunday.

May 2-30—**Overview of Integral Medicine.** UCLA. Tuesday evenings.

May 3-4—**Pesticide Protection Seminar for Health Personnel.** Calif. Dept. of Health at Bakersfield. Wednesday-Thursday. 14 hrs. Contact: Laboratory Training Office, Dept. of Health, 2151 Berkeley Way, Room 338, Berkeley 94704. (415) 843-7900, ext. 260.

May 6—**Critical Care Medicine—7th Annual Symposium.** South Coast Community Hospital, South Laguna. Saturday. Contact: Sol Sloan, MD, FACP, Dir. of Med. Ed., South Coast Community Hosp., 31872 Coast Highway, South Laguna 92677. (714) 499-1311, ext. 136.

May 12-13—**Alumni Days.** UCSF. Friday-Saturday.

May 12-14—**Resources in Human Sexuality.** National Sex Forum and Institute for Advanced Study of Human Sexuality at Towne House, Fresno. Friday-Sunday. 15 hrs. $110. Contact: Cont. Ed., Nat'l Sex Forum, 1523 Franklin St., San Francisco 94109. (415) 928-1133 or (213) 990-0774.

May 13—**Clinical Pharmacology.** STAN and Palo Alto Medical Clinic at STAN. Saturday. $15.

May 13-14—**Aging.** UCLA. Saturday-Sunday. 11 hrs. $90.

May 15-21—**Diving Medicine.** UCSF at VA Hospital, Fresno. One week.

May 19-21—**Health Aspects of Human Sexuality.** Human Sexuality Program, UCSF. Friday-Sunday. Contact: John Holland, Human Sexuality Prog., UCSF, 350 Parnassus Ave., Suite 700, San Francisco 94143. (415) 666-4787.

May 20-21—**Human Sexuality.** DREW. Saturday-Sunday.

May 21-26—**Orthopaedic Symposium for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $225.

June 2-3—**Management of Medical Problems.** PMC. Friday-Saturday. 15 hrs.

June 2-3—**Psychosocial Care of the Dying Patient.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

June 3-4—**Human Sexuality.** DREW. Saturday-Sunday.

June 3-4—**Nutrition: Myths and Realities.** UCSF and Institute for the Study of Human Knowledge. Saturday-Sunday.

June 7-8—**Pesticide Protection Seminar for Health Personnel.** Calif. Dept. of Health at Holiday Inn, Carmel. Wednesday-Thursday. 14 hrs. Contact: Laboratory Training Office, Dept. of Health, 2151 Berkeley Way, Room 338, Berkeley 94704. (415) 843-7900, ext. 260.

June 7-9—**Dermatology for the Family Practitioner.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Friday. 14½ hrs. $100.

June 8-10—**Nutritional Care of the Hospitalized Patient.** UCSF. Thursday-Saturday.

June 8-10—**Development of Occupational Health and Safety Services.** PMC. Thursday-Saturday.

June 10-11—**Practical Infectious Diseases for the Primary Care Physician.** UCLA. Saturday-Sunday.

June 16-18—**San Diego Chapter, California Academy of Family Physicians—22nd Annual Postgraduate Symposium.** Town and Country Hotel, San Diego. Friday-Sunday. 15 hrs. Contact: Don Wilson, MD, 233 A St., Suite 1005, San Diego 92101.

June 17-18—**Practical Applications of Biofeedback in the Health Sciences—5th Annual Seminar.** UCLA at Hyatt Hotel, Los Angeles Airport. Saturday-Sunday. 12½ hrs. $185.

June 18-24—**Family Practice Refresher Course—9th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. Sunday-Saturday.

June 20—**Hypertension—Rationale for Appropriate Work-Up and Advances in Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

July 10-21—**Intensive Workshop in Sex Therapy Skills.** UCSF Human Sexuality Program. Two weeks. $400. Contact: Human Sexuality Program, 350 Parnassus, No. 700, San Francisco 94143. (415) 666-4787.

July 22-25—**Allergy and Clinical Immunology for Non-Allergist Physicians.** American Assn. for Clinical Immunology and Allergy at Newporter Inn, Newport Beach. Saturday-Tuesday. 26 hrs. $260. Contact: AACIA, P.O. Box 912, Omaha, NE 68101. (402) 551-0801.

July 31-August 11—**Intensive Workshop in Sex Therapy Skills.** See above, July 10-21.

August 12-23—**Annual Postgraduate Refresher Course.** USC at Hawaii. 12 days.

August 13-18—**Family Practice Refresher Course—6th Annual.** UCD at Del Monte Hyatt House, Monterey. Saturday-Thursday. 30 hrs. $225.

September 25-28—**American Academy of Family Physicians.** Brooks Hall, San Francisco. Monday-Thursday. Contact: AAFP, 1740 W. 92nd St., Kansas City, MO 64114.

Audio-Digest Foundation. A nonprofit educational subsidiary of the California Medical Association. Twice-a-month tape-recorded summaries of leading national meetings. Services by subscription in: Anesthesiology, Family Practice, Internal Medicine, Obstetrics/Gynecology, Ophthalmology, Otorhinolaryngology, Pediatrics, Psychiatry, Surgery. ($90.00 per year for 24 one-hour cassettes or reels.) New catalog of lectures and panel discussions in all areas of medical practice also available, as well as cassette album condensations of the following 1977 specialty meetings: postgraduate courses from the annual meeting of the American Psychiatric Assn., workshops from the annual meeting of the American College of Physicians, and postgraduate courses from the annual sessions of the American College of Obstetricians and Gynecologists. For further information on subscriptions, catalogs and special courses, contact Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

Health Research Group of the American Institutes for Research. A not-for-profit research corp. CME research project seeks physician input. Physicians in general or family practice in non-urban areas of Calif. may be contacted to participate in a major research project on development of a continuing medical education system for doctors in office practice. Project will offer, without charge, up to 30 hrs. Category I credit in return for trying out and critiquing a newly developed set of instructional materials. These materials, entitled "Management of Adult Asthma: for General and Family Physicians," and the delivery system to be tried out were developed by the Health Research Group of the American Institutes for Research under contract to the National Heart, Lung, and Blood Insitute/National Institutes of Health. Contact: Muriel H. Bagshaw, MD, Project Dir., Health Research Group, American Institutes for Research, P.O. Box 1113, Palo Alto 94302. (415) 493-3550.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

May 4-7—**Oregon Academy of Family Practice Annual Scientific Assembly and Northwest Regional Scientific Assembly.** Jantzen Beach Thunderbird, Portland. Contact: Skippie Patterson, Oregon Academy of Family Physicians, 2153 SW Main, Portland 97205.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

May 31-June 3—**Oregon Society of Internal Medicine and Oregon Chapter, American College of Physicians Annual Meeting.** Salishan Lodge, Gleneden Beach. Contact: Joyce Gullixson, Oregon Society of Internal Medicine, 5210 SW Corbett Avenue, Portland 97201.

PEDIATRICS

May 11-13—**State Pediatric Society Annual Meeting.** Red Lion Motor Inn, Medford. Contact: Neil R. West, MD, 927 NW Grant Avenue, Corvallis 97330.

OF INTEREST TO ALL PHYSICIANS

April 27—**Circuit Course Program on Disorders of the Lower G.I. Tract.** Recreation Cafe, The Dalles. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 3—**Circuit Course Program on Current Problems in Pediatrics.** Douglas Community Hospital, Roseburg. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 4—**Circuit Course Program on Current Problems in Pediatrics.** Thunderbird Courtel, Coos Bay. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 12-13—**The Special Problems of the Injured Worker.** Cosmopolitan Airtel, Portland. Contact: NW Pain Center, 10615 SW Cherry Blossom Drive, Portland 97216.

May 17—**Circuit Course Program on Causes and Prevention of Stroke.** Presbyterian Inter-Community Hospital, Klamath Falls. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 18—**Circuit Course Program on Office Gynecology.** St. Charles Medical Center, Bend. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 18—**Circuit Course Program on Current Problems in Pediatrics.** Pacific Communities Hospital, Newport. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 25—**Circuit Course Program on Current Problems in Pediatrics.** Josephine General Hospital, Grants Pass. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 31—**Circuit Course Program on Disorders of the Lower G.I. Tract.** Columbia Memorial Hospital, Astoria. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

April 21-22—**First Annual Spring Medical-Surgical Conference.** Friday-Saturday, Elks Club, Lewiston, Idaho. 14 hrs. Fee: Before Apr. 1, $75; after Apr. 1, $90. Contact: Kenneth L. Judy, MD, St. Joseph's Hospital, P.O. Box 816, Lewiston, ID 83501. (208) 743-2511.

April 24-25—**Gynecologic Oncology—Univ. of Wash. Obstetrics and Gynecology Program in Idaho and Washington.** Monday, April 24, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391. Tuesday, April 25, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 24-25—**Pulmonary Disease, Part II—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, April 24, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, April 25, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

April 26—**Pacemaker Indications, Selection and Follow-up—Univ. of Wash. General Medicine Program in Anacortes, Washington.** Contact: Harry Eiesland, MD, 24th and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

April 26-28—**Interpretation of Cardiac Data, Valvular Heart Disease—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, April 26, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, April 27, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, April 28, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

(Continued on Page 34)

Brief Summary of Prescribing Information
Combined TEGOPEN® (cloxacillin sodium)
Capsules and Oral Solution
For complete information, consult Official Package Circular. (12) TEGOPEN 9/11/75
Indications: Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)
Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.
Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.
Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.
Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.
Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.
Contraindications: A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.
Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.
There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.
Safety for use in pregnancy has not been established.
Precautions: The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.
As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.
Adverse Reactions: Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.
Usual Dosage: Adults: 250 mg. q.6h.
Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.
N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.
Supplied: Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100. Oral Solution—125 mg. 5 ml. in 100 ml. and 200 ml. bottles.

BRISTOL®
BRISTOL LABORATORIES
Division of Bristol-Myers Company
Syracuse, New York 13201

IN THE LOS ANGELES AREA, STAPH RESISTANCE HAS NOW REACHED 80%.*

*resistance to penicillin G among community-acquired staph infections. Data on file, Bristol Laboratories.

WHEN YOU CAN'T RULE OUT STAPH, CONSIDER

TEGOPEN®
(cloxacillin sodium)

..."THE PENICILLIN OF TODAY"

- Effective against nonpenicillinase-producing staphylococci, beta-hemolytic streptococci, and pneumococci.†

†NOTE: The choice of Tegopen should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates that the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semisynthetic penicillin. The clinical significance of *in vitro* data is unknown.

- 10 times more active against strep than staph.
- Well absorbed from the G.I. tract.‡

‡Maximum absorption occurs when Tegopen is taken on an empty stomach, preferably 1-2 hrs. before meals.

Please see brief summary for prescribing information.

(Continued from Page 32)

May 1-4—**Pediatric Orthopaedics—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Monday, May 1, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Tuesday-Wednesday, May 2-3, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, May 3-4, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 5-6—**ENT Head and Neck.** Friday-Saturday. Glasier Auditorium, Swedish Hospital and Medical Center, Seattle. Contact: Dept. of Med. Ed., Swedish Hospital and Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2266.

May 8-9—**Advances in Contraception—Univ. of Wash. Obstetrics and Gynecology Program in Idaho and Washington.** Monday, May 8, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391. Tuesday, May 9, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 11-12—**Practitioner's Approach to Renal Disease.** Thursday-Friday. Virginia Mason Medical Center, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 12-14—**Pacific Northwest Radiological Society Annual Meeting.** Friday-Sunday. Empress Hotel, Victoria, BC, 10 hrs. Contact: Henry Jackh, MD, 140-1900 Richmond Ave., Victoria, BC, Canada V8R-4R2.

May 19-20—**Medical Applications of Diagnostic Ultrasound.** Friday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 22-23—**Radiologic Aspects of Renal Disease—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, May 22, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, May 23, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

May 24-26—**Clinical Rheumatology—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, May 24, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, May 25, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, May 26, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

June 2—**Management of Acute Medical Problems.** Friday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. Fee: $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 5-6—**Infertility—Univ. of Wash. Obstetrics and Gynecology Program in Idaho and Washington.** Monday, June 5, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391. Tuesday, June 6, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

June 7-9—**Osteoporosis and Metabolic Bone Disease Scanning—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, June 7, Great Falls. Contact: Sidney Pratt, MD, Box 2829, Great Falls, MT 59403. (406) 453-1491. Thursday, June 8, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, June 9, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

June 8-10—**Clinical Genetics—American College of Obstetricians and Gynecologists.** Thursday-Saturday. Washington Plaza Hotel, Seattle. 25 ACOG cognates. Fee: ACOG Fellows and Junior Fellows, $175; all others, $225. Contact: Morton Stenchever, MD, Chrmn., Dept. Ob-Gyn, School of Medicine, RH-20, University of Washington, Seattle, WA 98195. (206) 543-3580.

June 26-27—**Inflammatory Bowel Disease—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, June 26, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, June 27, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

July 20-22—**Cardiology Symposium: American College of Chest Physicians—Pacific Northwest Chapter.** Thursday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

August 17-18—**Difficult Problems in Pediatric Orthopaedics.** Thursday-Friday. Washington Plaza Hotel, Seattle. 14 hrs. Fee: $150. Contact: Dept. of Orthopaedics, ZC-10, Childrens Orthopedic Hospital and Medical Center, P.O. Box C5371, Seattle, WA 98105. (206) 634-5250.

Index to The Western Journal of Medicine Advertising

Bank of America
Business Services 3
Professional/Executive 11

Beth Israel Hospital
Aspen Mushroom Conference 25

Breon Laboratories, Inc.
Spirometer 35, 36

Bristol Laboratories
Tegopen 32, 33

Classified 22, 24, 25

Defenders Mutual Insurance Company 23

Eli Lilly
Kefzol 21

Endo Laboratories
Percodan 28, 29

Geigy Pharmaceuticals
Brethine 8, 9, 10

Hawaiian Conference Services
Seminar in Pathology 25

Mead Johnson Laboratories
Colace/Quibron 17, 18, 19, 20

Medical World News 7

Merck Sharp & Dohme
Hydrodiuril 14, 15

Presto Foods
Mocha Mix 12

Roche Laboratories
Librax ..... 2nd Cover, 1, 2
Valium ..... 3rd and 4th Covers

Smith, Kline & French Co.
Dyazide 5

The Upjohn Co.
Tolinase 6

Warren-Teed Laboratories, Inc.
Kaon Elixir 13

White Memorial Medical Center/Loma Linda University School of Medicine
Symposium: Surgical Management of the Traumatized Patient 16

THE WESTERN Journal of Medicine

VOLUME 128 • NUMBER 5 MAY 1978

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON

MAY 26 1978

377 *Pulmonary Embolectomy*
ARGUN SAYLAM, MD; JOAO Q. MELO, MD; AFTAB AHMAD, MD; RICHARD D. CHAPMAN, MD; JAMES A. WOOD, MD, and ALBERT STARR, MD

382 *Seminars in Virology: A Biological Perspective of Slow Virus Infection and Chronic Disease*
JOSEPH W. ST. GEME, JR., MD

390 *Blood Transfusion: Use and Abuse of Blood Components* D. GORDON JOHNSTON, MD

MEDICAL PROGRESS

399 *Adult Respiratory Distress Syndrome* THOMAS L. PETTY, MD, and JOHN H. NEWMAN, MD

SPECIALTY CONFERENCE

408 *An Approach to the Treatment of Asthma*
Participants: MICHAEL MELLON, MD; GARY I. INCAUDO, MD; STEPHEN KAHLER, MD; ROBERT N. HAMBURGER, MD, and WILLIAM L. NYHAN, MD, PhD
Pediatric Conference, Division of Pediatric Immunology and Allergy, Department of Pediatrics, University of California, San Diego, School of Medicine, and the University of California Medical Center, San Diego

MEDICAL STAFF CONFERENCE

419 *Crohn Disease—Newer Aspects of Etiology, Diagnosis and Therapy*
Chief Discussants: JOHN P. CELLO, MD, and RUEDI F. THOENI, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

428 *Ophthalmology—Epitomes of Progress*

EDITORIALS

434 • *Participatory Democracy and Health Care* • *Adult Respiratory Distress Syndrome—What To Do Until the Basic Scientist Comes* • *Medicine in Ponape* • *Management of Asthma*

CASE REPORTS

440 *Ipecac Poisoning* JAMES S. MISER, MD, and WILLIAM O. ROBERTSON, MD

443 *Legionnaires Disease Causing Adult Respiratory Distress Syndrome—Survival and Report of Open Lung Biopsy* RICHARD A. NUSSER, MD, and MITCHELL P. TARKOFF, MD

CORRESPONDENCE

449 • *More on 'The 11th Myth' About FDA* • *Gerontology and Geriatrics* • *Thoracic Outlet Syndrome* • *Outpatient Self-Administration of Parenteral Antibiotics*

MEDICAL EDUCATION

453 *A Medical Resident in Ponape* ALAN C. NELSEN, MD

MEDICAL JURISPRUDENCE

459 *Psychiatric Treatment—General Implications and Lessons from Recent Court Decisions in California* EDWARD RUDIN, MD, and RICK ZIMMERMAN, Esq

467 *Book Reviews* • *Books Received, see Advertising Page 6*

468 **NEVADA STATE MEDICAL ASSOCIATION ANNUAL MEETING, MAY 19-21, 1978**

469 *In Memoriam*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, ALASKA, MONTANA AND IDAHO**
(See Advertising Page 31)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association and the Nevada State Medical Association**

BOSTON
10 SHAT
NEW ENGLAND
11492-021 7
BOSTON

In acute cystitis,* effective antibacterial action...

in double strength form for added convenience and economy

*nonobstructed; due to susceptible organisms such as *E. coli*, *Klebsiella-Aerobacter*, staphylococcus, *Proteus mirabilis* and, less frequently, *Proteus vulgaris*

B.I.D. dosage improves compliance

Several studies have shown that the simpler the dosage regimen, the greater the patient compliance.[1,2] Gantanol (sulfamethoxazole) provides the convenience of simple *b.i.d.* dosage—and now double strength Gantanol DS tablets give your patients with acute cystitis the added convenience of taking only two tablets a day.

24-hour action against bacterial buildup

Lack of voiding during the hours of sleep permits bacterial multiplication in the bladder.[3] The slower excretion rate of Gantanol relative to short-acting sulfonamides allows for the maintenance of therapeutic blood levels on *b.i.d.* dosage, thus assuring 24-hour antibacterial activity and inhibiting nighttime bacterial buildup.

In a clinical study testing the efficacy of Gantanol *b.i.d.* against organisms most commonly responsible for acute cystitis, including *E. coli*, 81% of 406 patients tested achieved zero colonies/ml urine, 83% less than 1,000/ml and 88% less than 10,000/ml.[4]

Double Strength tablets

Gantanol DS tablets offer added convenience and economy for your patients with acute, nonobstructed cystitis. The simplified dosage regimen encourages patient compliance: 2 tablets (1 Gm each) STAT—then 1 tablet *b.i.d.* for 10 to 14 days.

Gantanol is contraindicated during pregnancy, the nursing period, and in infants under 2 months. During therapy, caution patients to maintain adequate fluid intake; perform frequent CBC's and urinalyses with careful microscopic examination.

References: 1. Gatley MS: *J R Coll Gen Pract 16*:39-44, July 1968. 2. Eklund LH, Wessling A: *Clin Ther 1*:81-89, Jan 1977. 3. Holloway WJ: *Consultant 17*:162-173, July 1976. 4. Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

2 tablets STAT, then only 1 tablet B.I.D.

Gantanol® DS
sulfamethoxazole/Roche
Double Strength Tablets

ROCHE

Please see brief summary of complete product information on following page.

Gantanol® DS
sulfamethoxazole/Roche
Double Strength Tablets

Before prescribing, please consult complete product information, a summary of which follows:
Indications: Acute, recurrent or chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter,* staphylococcus, *Proteus mirabilis* and, less frequently, *Proteus vulgaris*), in the absence of obstructive uropathy or foreign bodies. Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections. Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.
Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.
Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.
Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.
Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.
Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). *Usual adult dosage:* 2 Gm (2 DS tabs or 4 tabs or 4 teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.
Usual child's dosage: 0.5 Gm (1 tab or teasp.) /20 lbs of body weight initially, than 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.
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Subscription prices, $10 ($12 for foreign countries); student subscription $5 ($7 for foreign countries); single copies $1.25. WESTERN JOURNAL Circulation, 731 Market St., San Francisco, Ca 94103.

Volumes begin with the first of January and the first of July. Subscriptions may commence at any time.

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ISSN 0093-0415

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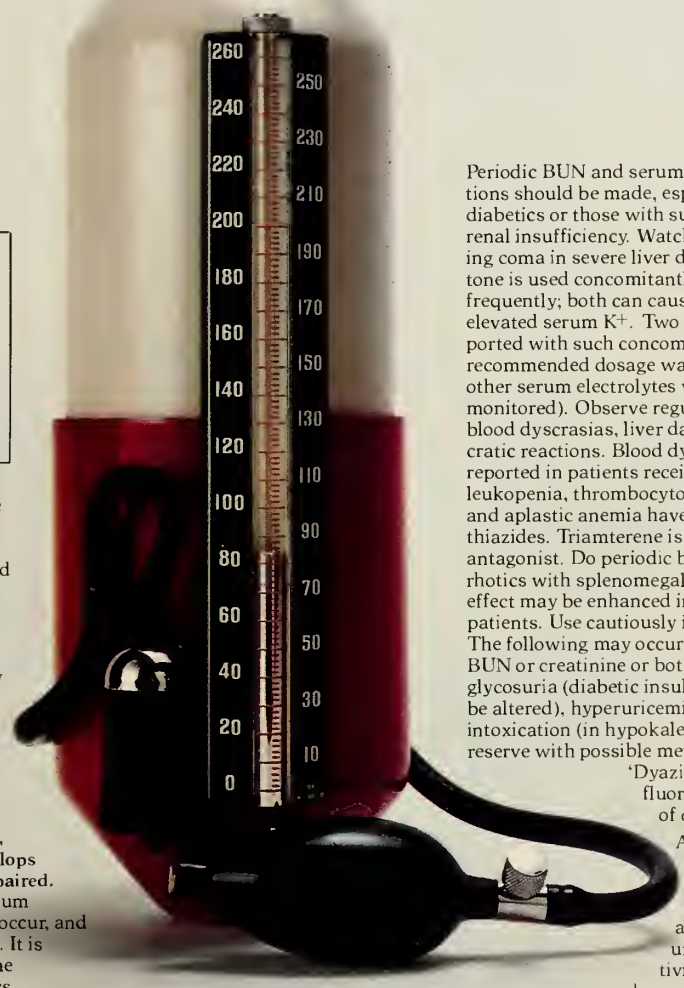

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* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ALVAREZ ON ALVAREZ—Walter Clement Alvarez, MD. Strawberry Hill Press, 616 - 44th Avenue, San Francisco (94221), 1977. 160 pages, $5.95 (Paperback). Distributed by Stackpole Books, Cameron & Kelker Sts., Harrisburg, PA 17105.

BASIC TECHNIQUES IN DIAGNOSTIC HISTOPATHOLOGY—Alexander Kennedy, MD, MRCPath, Consultant Pathologist, Sheffield Area Health Authority (Teaching); Formerly Senior Lecturer in Pathology, University of Sheffield, Visiting Assistant Professor in Surgical Pathology, University of Chicago, and Lecturer in Pathology, University of Liverpool. Churchill Livingstone-Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 117 pages, $9.50.

CARDIAC EMERGENCIES—Edited by Dean T. Mason, MD, Professor of Medicine; Professor of Physiology; Chief, Cardiovascular Medicine, University of California, Davis, School of Medicine, Sacramento Medical Center, Davis and Sacramento; President, American College of Cardiology; with 34 contributors. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1978. 408 pages, $29.50.

THE COMPULSIVE OVEREATER—Seven Steps to Thin Sanity—George F. Christians. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1978. 100 pages, $5.95.

COPEMAN'S TEXTBOOK OF THE RHEUMATIC DISEASES—Fifth Edition—Edited by J. T. Scott, MD, FRCP, Consultant Physician, Charing Cross and West London Hospitals, London; Honorary Physician and Head, Clinical Division, Kennedy Institute of Rheumatology, London. Churchill Livingstone/Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 1,080 pages, $65.00.

CURRENT PEDIATRIC DIAGNOSIS & TREATMENT—Fifth Edition—C. Henry Kempe, MD, Professor of Pediatrics and Microbiology; Henry K. Silver, MD, Professor of Pediatrics, and Donough O'Brien, MD, FRCP, Professor of Pediatrics, University of Colorado School of Medicine, Denver; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1978. 1,102 pages, $17.00.

EVERY WOMAN'S GUIDE TO HYSTERECTOMY—Taking Charge of Your Own Body—DeeDee Jameson, Assistant Professor of Early Childhood and Human Development, School of Home Economics, University of Vermont; and Roberta Schwalb, RN, CNM, Associate Professor of professional nursing, University of Vermont. Prentice-Hall, Inc., Publishers, Englewood Cliffs, NJ (07632), 1978. 152 pages, $8.95 (cloth); $3.95 (paperback).

FAMILY MEDICINE—Principles and Applications—Edited by Jack H. Medalie, MD, MPH, Professor and Chairman, Department of Family Medicine, Case Western Reserve University School of Medicine, Cleveland. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore (21202), 1978. 372 pages, $15.95.

FOR HEALTH'S SAKE—A Critical Analysis of Medical Care in the United States. Howard R. Grossman, MD, Chief of Professional Services and surgeon, Veterans Administration Hospital, Martinez, California. Pacific Books, Publishers, P.O. Box 558, Palo Alto, CA (94302), 1977. 221 pages, $8.95.

GENETIC EFFECTS ON AGING—Volume XIV in the Original Article Series: BIRTH DEFECTS: Proceedings of a Conference Held at the Jackson Laboratory, Sep 12-17, 1976, Sponsored by the National Foundation—March of Dimes—Editors: Daniel Bergsma, MD, Vice President for Professional Education, The National Foundation; David E. Harrison, PhD, Staff Scientist, The Jackson Laboratory, Bar Harbor, Maine; Associate Editor: Natalie W. Paul, The National Foundation. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1978. 550 pages, $50.00.

HANDBOOK OF TREATMENT OF MENTAL DISORDERS IN CHILDHOOD AND ADOLESCENCE—Editor: Benjamin B. Wolman, PhD, Professor of Clinical Psychology, Long Island University, and Editor-in-Chief, **International Encyclopedia of Psychiatry, Psychology, Psychoanalysis, and Neurology;** Co-Editors: James Egan, MD, and Alan O. Ross, PhD. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1978. 475 pages, $29.95.

OBESITY—Everything You Should Know But Have Never Been Told—John Erhardt, MD, Laguna Hills, CA. California Medical Press, 25132 Vespucci Rd., Laguna Hills, CA (92653), 1978. 129 pages, $6.00 (paperback).

RECENT ADVANCES IN CLINICAL IMMUNOLOGY—Edited by R. A. Thompson, MBE, MBBS, BSc, MRCP, MRCPath, Consultant Immunologist, Director, Regional Immunology Laboratory, East Birmingham Hospital; Senior Clinical Lecturer, Department of Experimenal Pathology, University of Birmingham. Churchill Livingston—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 299 pages, $25.00.

TOGETHER—A Casebook of Joint Practices in Primary Care—General Editor: Berton Roueché. National Joint Practice Commission, 35 E. Wacker Drive, Chicago (60601), 1977. 256 pages, $5.95 includes postage and handling. Orders must be prepaid to: NJPC/EPIC, 7383 Lincoln Ave., Chicago, IL 60646.

TOUCHE ROSS HEALTH CARE HORIZONS '77—New Technology . . . Increasing Costs . . . Constricted Revenues—Forty-fifth Annual Review of Hospital Operations. Copies are available without charge from Frank Transow, Touche Ross & Co., 3700 Wilshire Blvd., Los Angeles, CA 90010.

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Percocet®-5 CII

DESCRIPTION Each tablet of PERCOCET®-5 contains 5mg oxycodone hydrochloride (WARNING: May be habit forming), 325mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS.

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November 1977 EDO 148P

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Acetaminophen with the narcotic difference

Reliable oral narcotic analgesia...

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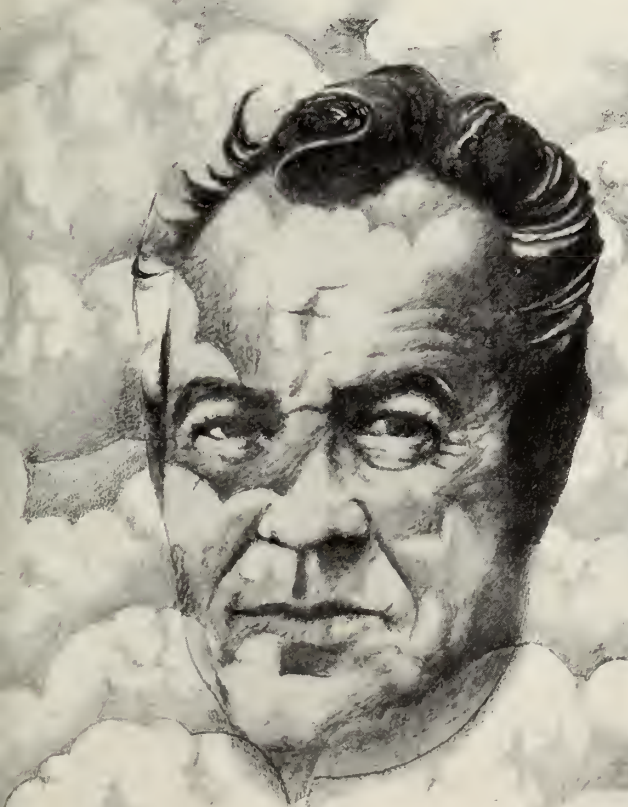
The usual dose of PERCOCET®-5 is one tablet every six hours, providing convenience and economy for your patients. PERCOCET®-5 is ideally suited for your patients with aspirin sensitivity, with hemostatic disturbance, with peptic ulcer or on anticoagulation therapy.



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Percocet®-5

each scored tablet contains 5 mg oxycodone HCl (WARNING: may be habit forming) and 325 mg acetaminophen

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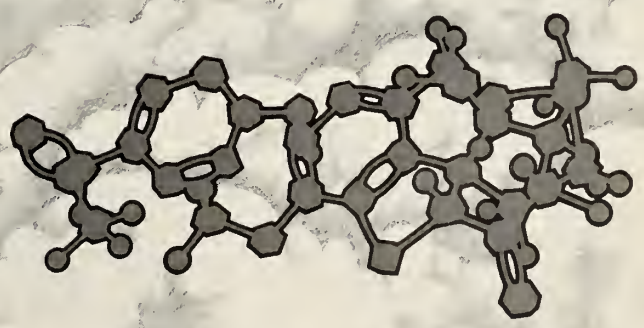
When aspirin is contraindicated.



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Please see facing page for Brief Summary of prescribing information.

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- Catapres lowers blood pressure promptly.
- No contraindications.
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The next 20 years*

- Lowered blood pressure.
- Little impotence, depression or postural hypotension.
- No fatal hepatotoxicity in over a decade of worldwide use.
- Broad therapeutic dosage range to keep step with changing dosage needs over the years.

*Tolerance may develop in some patients, necessitating a reevaluation of therapy.

For full details on adverse reactions, warnings and precautions, see brief summary of the prescribing information on last page of this advertisement.

Catapres® (clonidine HCl)
For Step 2 in
Hypertension

HYPERTENSION

A New Vision of Catapres® (clonidine HCl)

Tablets of 0.1 and 0.2 mg

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Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment hypertension. As an antihypertensive drug, Catapr (clonidine hydrochloride) is mild to moderate in pc It may be employed in a general treatment progran with a diuretic and/or other antihypertensive agen as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findin animals, and since information on possible advers effects in pregnant women is limited to uncontrolle clinical data, the drug is not recommended in wom who are or may become pregnant unless the poten benefits outweigh the potential risk to mother and *Usage in Children:* No clinical experience is availa with the use of Catapres (clonidine hydrochloride) children.

Precautions: When discontinuing Catapres (clonid hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood press and associated subjective symptoms such as nerv ness, agitation, and headache. Patients should be instructed not to discontinue therapy without consu their physician. Rare instances of hypertensive enc lopathy and death have been recorded after cessat of clonidine hydrochloride therapy. A causal relatio ship has not been established in these cases. It ha been demonstrated that an excessive rise in blood sure, should it occur, can be reversed by resumptio of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machi or driving, should be advised of the sedative effect This drug may enhance the CNS-depressive effects alcohol, barbiturates and other sedatives. Like any agent lowering blood pressure, clonidine hydrochlo should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care patients treated with Catapres (clonidine hydrochlo should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-relate abnormal ophthalmologic findings have been recor with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increa in the incidence and severity of spontaneously occu ring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions ar dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reporte Generally these effects tend to diminish with contin therapy. The following reactions have been associat with the drug, some of them rarely. (In some instan an exact causal relationship has not been establish These include: Anorexia, malaise, nausea, vomiting parotid pain, mild transient abnormalities in liver fu tion tests; one report of possible drug-induced hepa titis without icterus and hyperbilirubinemia in a pat receiving clonidine hydrochloride, chlorthalidone, a papaverine hydrochloride. Weight gain, transient el tion of blood glucose, or serum creatine phosphokir congestive heart failure, Raynaud's phenomenon; v dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and me depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associate with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, som lence, diminished or absent reflexes and vomiting fo lowed the accidental ingestion of Catapres (clonidir hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all ef fects of Catapres (clonidine hydrochloride) overdosa

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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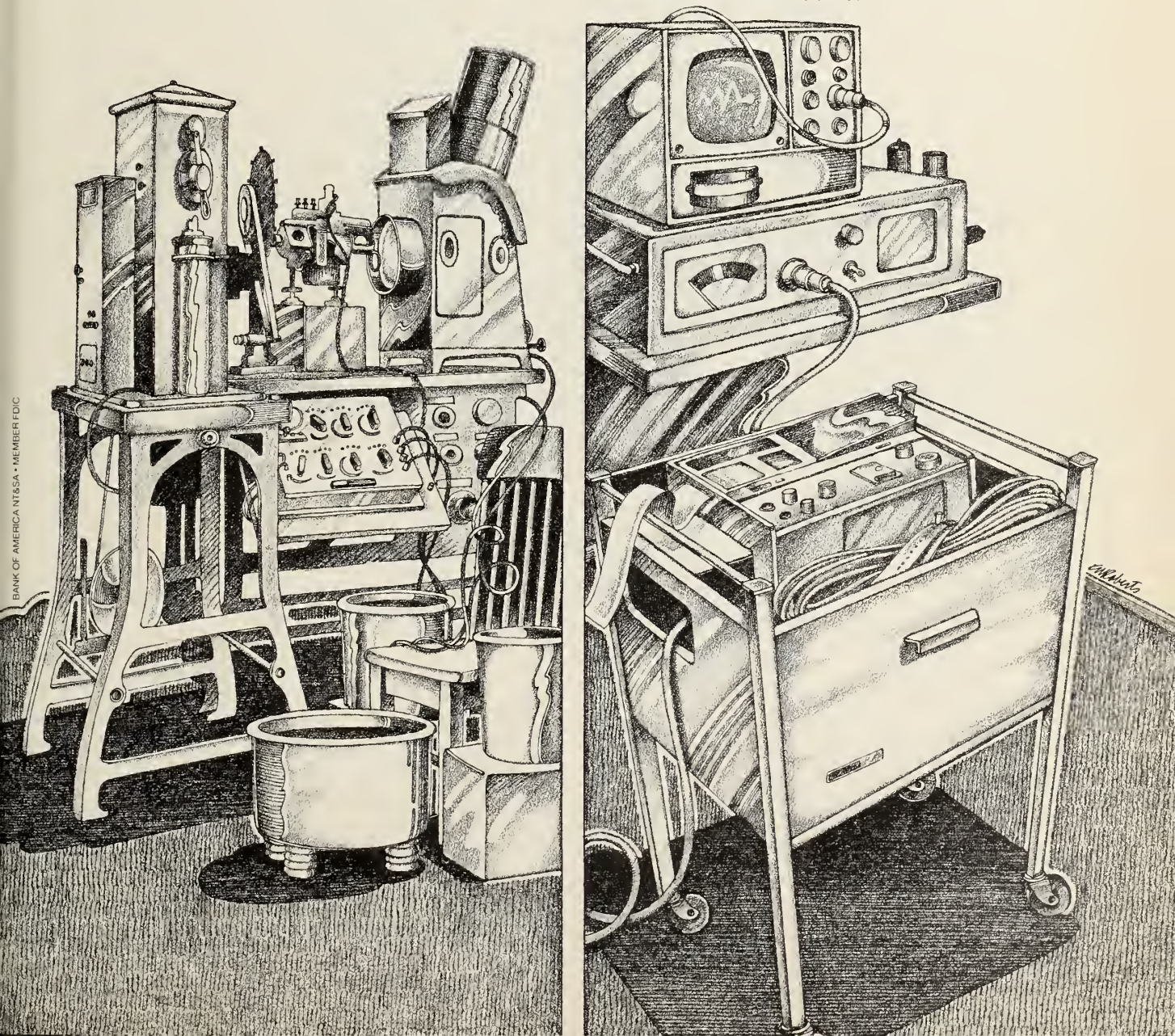

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BRIEF SUMMARY
Kaon Tablets/Kaon Elixir

KAON® (potassium gluconate) TABLETS

Description: Each sugar-coated tablet supplies 5 mEq. of elemental potassium (as potassium gluconate 1.17 Gm.). Kaon Tablets are sugar coated, not enteric coated, which favors dissolution in the stomach and absorption before reaching the small intestine where the lesions with enteric potassium chloride have occurred. The sugar coating merely adds to palatability and ease of swallowing, not to delay absorption as does the enteric coating.
Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. It may be used in the treatment of cardiac arrhythmias due to digitalis intoxication.
Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.
Warning: There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides or certain other oral diuretics. These small-bowel lesions have caused obstruction, hemorrhage and perforation. Surgery was frequently required and deaths have occurred. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Coated potassium tablets should be used only when adequate dietary supplementation is not practical.
Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. With normal kidney function, it is difficult, therefore, to produce potassium intoxication by oral administration. However, potassium supplements must be administered with caution, since the amount of the deficienc or daily dosage is not accurately known. Frequent checks of the clinical status of the patient and periodic ECG and/or serum potassium levels should be made. High serum concentra-

1954
1978

Time is the test of all things

tions of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

In hypokalemic states, especially in patients on a salt-free diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation. In these circumstances, Kaon (potassium gluconate) should be supplemented with chloride. Ammonium chloride is an excellent source of chloride ion (18.7 mEq. per Gram), but it should not be used in patients with hepatic cirrhosis where ammonium salts are contraindicated. Other sources for chloride are sodium chloride and Diluted Hydrochloric Acid, U.S.P.

It should also be kept in mind that ammonium cycle cation exchange resin, sometimes used to treat hyperkalemia, should not be administered to patients with hepatic cirrhosis.

Adverse Reactions: Nausea, vomiting, diarrhea and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias and heart block. Hyperkalemia may exhibit the following electrocardiographic abnormalities: disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

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Description: Each 15 ml. (tablespoonful) supplies 20 mEq. of elemental potassium (as potassium gluconate, 4.68 Gm.) with saccharin and aromatics. Alcohol 5%.

Indications: See Kaon Tablets.

Precautions: See Kaon Tablets.

In hypochloremic alkalosis, potassium replacement with potassium chloride (e.g., Kaochlor® 10% Liquid) may be more advantageous than with other potassium salts.

Adverse Reactions: See Kaon Tablets.

Overdosage: See Kaon Tablets.

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***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:
Possibly Effective:
1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.
Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.
Dosage and Administration: Oral: 10 to 20 mg., three or four times daily.
Intramuscular: 5 to 10 mg. (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.
Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.
Parenteral administration is not recommended in the presence of hypotension or tachycardia
Intravenous administration should not be given because of increased likelihood of side effects.
Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.
Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted.
Administration of single dose of 10 mg. intramuscularly may result in hypotension and tachycardia. These symptoms are more pronounced in higher doses. For these reasons single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed.
Supplied: Tablets, 10 mg., bottles of 100, 1000, 5000 and Unit Dose; Tablets, 20 mg., bottles of 100, 500, 1000, 5000 and Unit Dose; Injection, 10 mg. per 2 ml. ampul, box of six 2 ml. ampuls.

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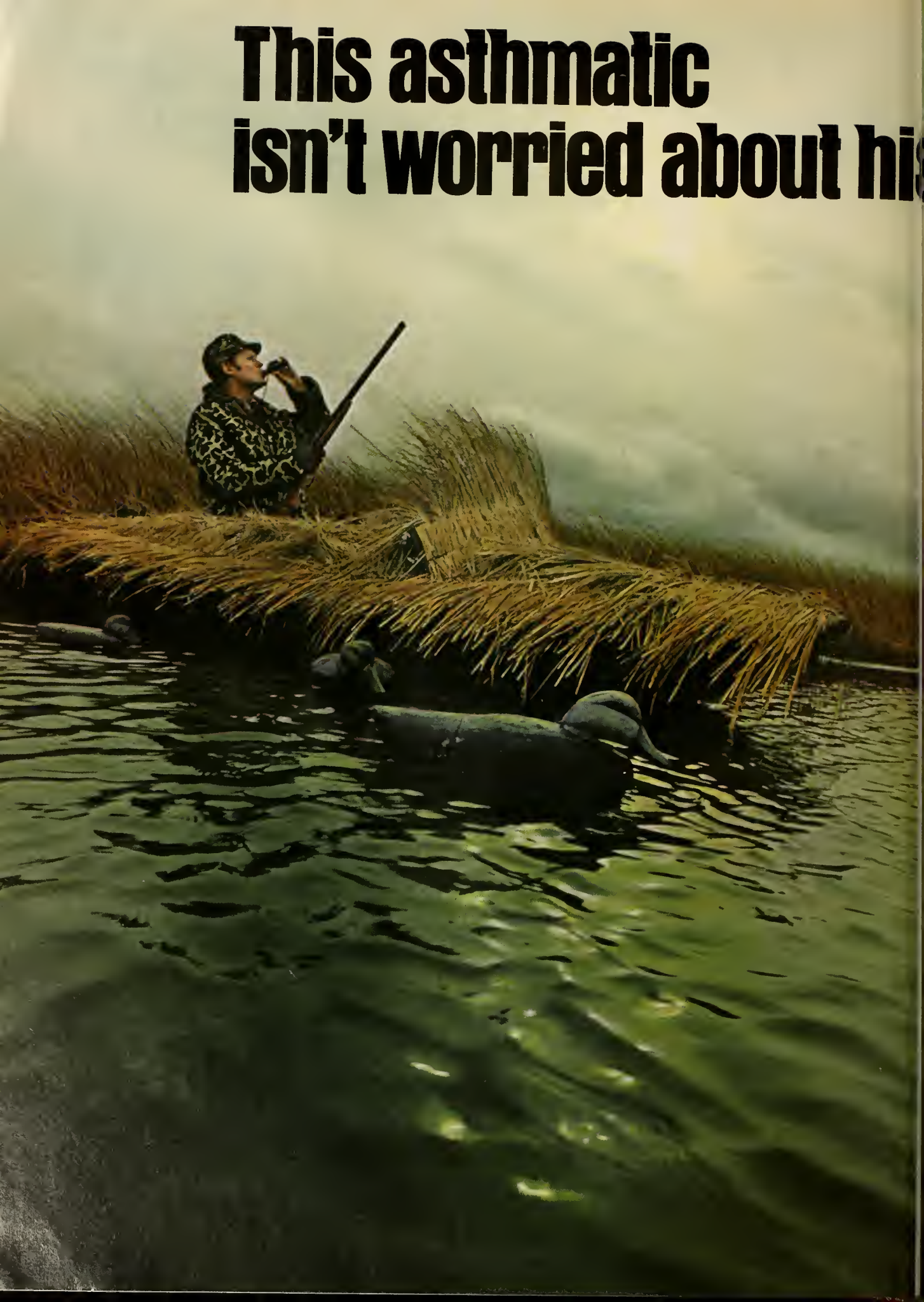
This asthmatic isn't worried about his



ext breath...

he's active
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Each capsule or tablespoonful (15 ml) elixir contains theophylline (anhydrous) 150 mg and glyceryl guaiacolate (guaifenesin) 90 mg. Elixir: alcohol 15%

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Quibron may give the asthmatic up to eight hours of bronchodilation with each dose and provides the high dosages of theophylline which are now believed necessary to keep patients free of acute attacks and chronic wheezing.

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Today's more efficient usage of theophylline includes individualizing dosage and monitoring serum theophylline levels. The usual recommended dosages of Quibron are: Adults—1 to 2 capsules or tablespoonfuls every 6 to 8 hours; dosage may be cautiously adjusted upward when necessary to a maximum of 2000 mg theophylline per 24 hours. Children under 12—4 to 6 mg theophylline per kg/body weight every 6 to 8 hours; dosage may be cautiously adjusted up to 9 or 10 mg/kg every 6 hours.

Now, for the asthmatic who requires high-dose theophylline therapy for therapeutic serum concentrations

Mead Johnson Pharmaceutical Division announces

QUIBRON®-300

Each capsule contains 300 mg theophylline (anhydrous) and 180 mg glyceryl guaiacolate (guaifenesin)

For Brief Summary, please see the last page of this advertisement.

QUIBRON®-300

Each capsule contains 300 mg theophylline (anhydrous) and 180 mg glyceryl guaiacolate (guaifenesin)

The new high-dose theophylline capsule... for dependable theophylline therapy when products of lower dosage do not adequately control asthma symptoms.

Specially formulated

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Quibron-300 is appropriate therapy for asthma patients whose symptoms are not adequately controlled on lower doses of theophylline, particularly for patients whose theophylline dosage has been adjusted upward to achieve therapeutic serum levels. In one study,[1] an average peak increase in FEV_1 of 35% was demonstrated after a single dose equivalent to one Quibron-300 capsule, and significant improvement in this pulmonary function lasted for nearly eight hours after administration.

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One Quibron-300 capsule q6-8h yields therapeutic serum levels (10-20 mcg/ml) in many adults. With a single dose, more than 75% of patients achieved serum levels potentially providing clinical benefit (5-15 mcg/ml). Half-life of theophylline varies widely from patient to patient, making monitoring of theophylline therapy important. Patient response may be monitored clinically if blood levels are not available as long as dosage does not exceed 1200 mg in 24 hours for adults.

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The simple, convenient dosage of new Quibron-300—one capsule every six to eight hours—makes it easy for patients to comply with high-dose regimens often required to achieve therapeutic serum levels. Quibron-300 capsules may provide maximum therapeutic value with maximum convenience. In fact, the switch from a low-dose to a high-dose regimen may be accomplished by merely switching capsules, by stepping up to Quibron-300 capsules.

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Adverse reactions to theophylline are related to serum levels and are usually not a problem at concentrations below 20 mcg/ml. Of 45 patients studied[1] after a single dose, only seven reported adverse reactions. The most common reaction was a feeling of lightheadedness by three of these seven patients.

Reference 1 Data on file, Mead Johnson Pharmaceutical Division.

Indications: For the symptomatic treatment of bronchospastic conditions such as bronchial asthma, asthmatic bronchitis, chronic bronchitis, and pulmonary emphysema.
Dosage: Quibron—Adults: 1-2 capsules or 1-2 tablespoonfuls elixir every 6-8 hours. Children under 12: 4-6 mg theophylline/kg body weight every 6-8 hours.
Quibron-300— Adults: 1 capsule every 6-8 hours.
Theophylline dosage may be cautiously increased to 2000 mg/24 hour in adults and 9 or 10 mg/kg every 6 hours in children. Monitoring of serum theophylline levels at higher dosages is recommended.
Precautions: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other xanthine derivatives concurrently. Use in case of pregnancy only when clearly needed.
Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 μg/ml.
How Supplied: Quibron Elixir: Bottles of 1 pint and 1 gallon. Quibron Capsules: Bottles of 100 and 1000 and unit-dose packs of 100. Quibron-300 Capsules: Bottles of 100.

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MJL 7-4280

THE WESTERN
Journal of Medicine

Refer to: Saylam A, Melo JQ, Ahmad A, et al: Pulmonary embolectomy. West J Med 128:377-381, May 1978

Pulmonary Embolectomy

ARGUN SAYLAM, MD; JOAO Q. MELO, MD; AFTAB AHMAD, MD; RICHARD D. CHAPMAN, MD; JAMES A. WOOD, MD, and ALBERT STARR, MD, *Portland, Oregon*

Embolectomy was carried out in eight patients with pulmonary emboli. Angiographic diagnosis was obtained in six, and in two cases pulmonary angiography could not be done because of the very critical condition of the patients. In the latter two, diagnosis was made based only on clinical findings. Two patients died in the operating room (25 percent). Six patients were discharged in good condition.

It is emphasized that pulmonary embolectomy should be done in cases of pulmonary emboli when a clinical status of shock is present (systolic blood pressure less than 80 mm of mercury and the patient in low cardiac output syndrome) and when there is no response to medical treatment regardless of the degree of obstruction in the pulmonary arterial tree.

PULMONARY EMBOLISM is a life-threatening pathologic condition. It has been estimated that in the United States a total of 193,795 patients are still dying each year due to this complication.[1] The use of embolectomy in the treatment of pulmonary emboli was first suggested by Trendelenburg in 1908,[2] successfully carried out for the first time by Kirschner in 1924 with the use of inflow occlusion technique,[3] and accomplished with the help of extracorporeal circulation by Sharp[4] and Cooley and associates[5] in the early 1960's. The proper role of this procedure still needs to be defined precisely.[6,7]

This report is based upon our experience during the past five years in an active cardiac unit. The role of emergency surgical operation in a certain subset of patients with pulmonary embolism is hereby established.

From Department of Cardiovascular and Pulmonary Surgery, St. Vincent Hospital and Medical Center, Portland, Oregon.

Submitted, revised, November 10, 1977.

Reprint requests to: Albert Starr, MD, 9155 S. W. Barnes Road, Portland, OR 97225.

Patients and Methods

In eight patients with a diagnosis of pulmonary embolism, operations were done between 1972 and 1977 at the University of Oregon Health Sciences Center affiliated with St. Vincent Hospital and Medical Center in Portland, Oregon. Details of these cases are tabulated in Table 1.

The patients had low cardiac output syndrome with blood pressure less than 80 mm of mercury. Dopamine hydrochloride and isoproterenol hydrochloride infusions were used to maintain a satisfactory blood pressure. Heparin infusion (1,000 units per hour) and dexamethasone administration (4 mg every four hours) were also started during the preoperative period. Patients had poor response to medical treatment.

Preoperative pulmonary angiography could not be done in two patients because of their clinical condition (in one cardiac arrest occurred and the patient was resuscitated on the way to the operating table and in the other severe shock

and low cardiac output syndrome developed), where presumptive diagnosis was made based on clinical findings. Pulmonary angiography was done in six cases (see Figures 1 and 2), showing diffuse bilateral multiple ischemic areas in four patients (cases 4, 5, 6 and 8), ischemic left lung in one patient (case 2) and ischemic right lung, especially in the middle and lower lobes, in one patient (case 7).

In four patients pulmonary embolism occurred during the early postoperative period after coronary artery surgical operation. In three of the four no anticoagulants were given after open heart operation (case 1, 2 and 4) and in one (case 3) oral administration of an anticoagulant [warfarin sodium (Coumadin®)] was begun on the second postoperative day. In all the patients in whom coronary artery operations were done, digitalis was given during the postoperative period.

In two patients pulmonary embolism developed after abdominal operations. Two other patients did not indicate any history of recent operation, but they were in bed with lack of activity due to underlying conditions (acute cholecystitis in one, and senile dementia in the other). Signs of phlebitis were observed only in one patient (case 3).

Operative Technique

Operations were done using cardiopulmonary bypass. The chest was opened with a median

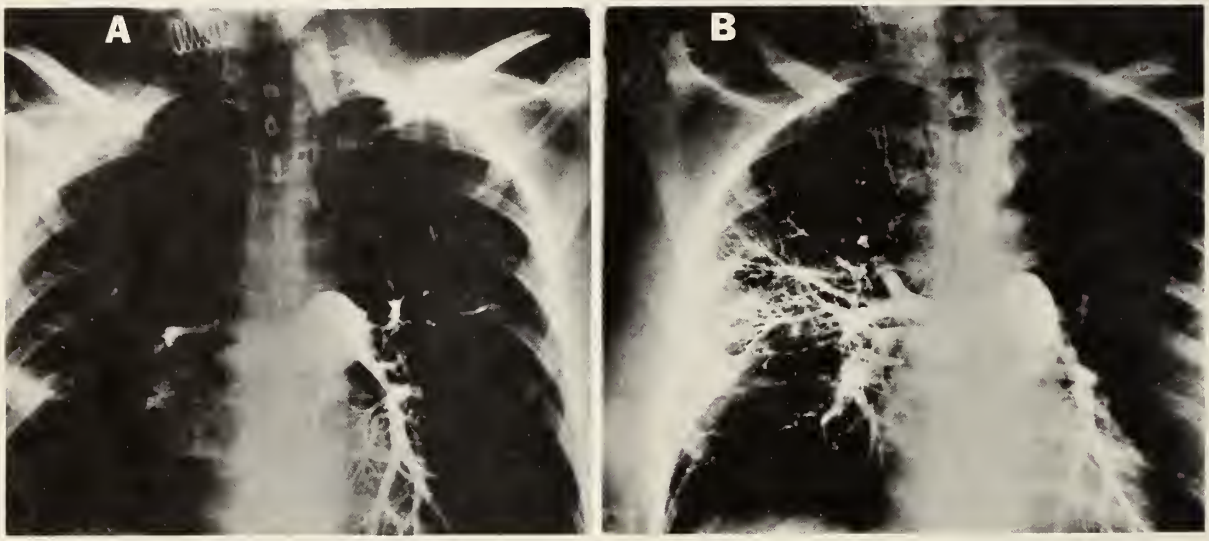

Figure 1.—(case 6) **A**, Left pulmonary arteriography; **B**, Right pulmonary arteriography.

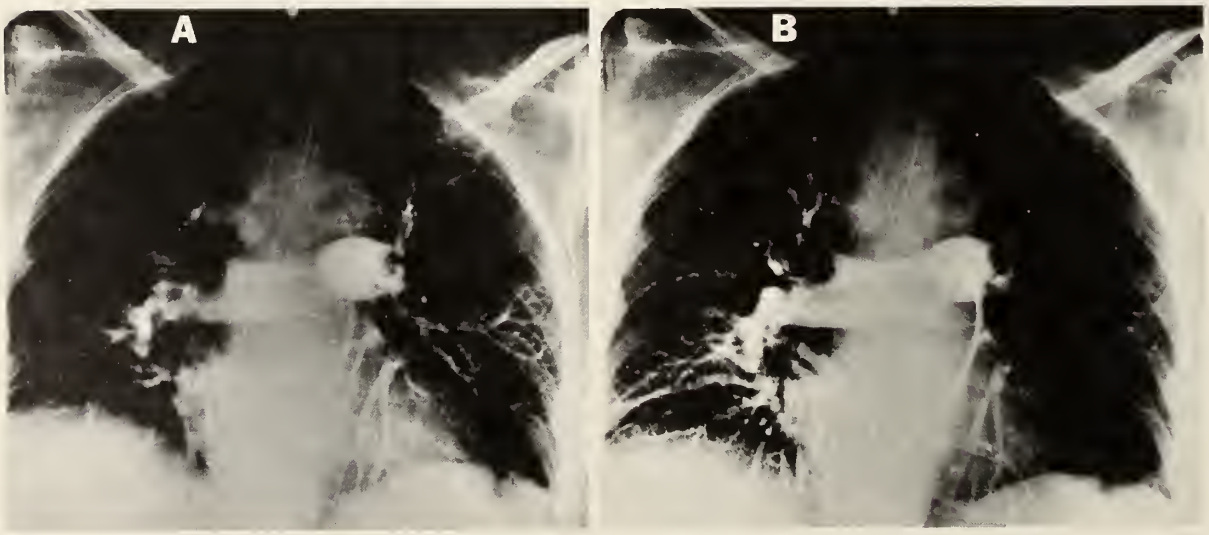

Figure 2.—(case 8) **A**, Left pulmonary arteriography; **B**, Right pulmonary arteriography.

sternal incision and tapes were placed around the cavae. The heart was fibrillated with the help of epicardial wires after institution of bypass, and longitudinal pulmonary arteriotomy was done after tightening of the tapes around the cavae. Clots were removed from the pulmonary artery by curved forceps and suction. Both pleural cavities were opened, the lungs massaged and milked from periphery to hilus and small clots coming from the periphery were sucked out from the pulmonary artery. The pulmonary arteriotomy was closed, the heart defibrillated, and the patient was weaned off bypass gradually.

Thrombosis of coronary bypass grafts was found in one patient in whom pulmonary embolectomy was done, and thrombectomy of the grafts was also carried out with Fogarty catheters at the same time.

Postoperative Status and Results

Two patients died on the operating table (25 percent mortality) and the other patients did well after the operation (see Table 1). In one patient tracheostomy was needed in the postoperative period. Pulmonary pressures were monitored in the cardiac recovery room continuously by a Swan-Ganz catheter introduced into the pulmonary artery during the preoperative period. Digitalis was administered to all patients during the postoperative period, heparin drip infusion (1,000 units per hour) was maintained for a week after the operation and then anticoagulation with warfarin sodium was carried out for three months. Dopamine hydrochloride and isoproterenol hydrochloride infusions were done for a mean of six days (changing between 2 and 15 days) to support the heart during the postoperative period. Dexamethasone was used postoperatively only in two cases for one week.

In two patients additional operations were done during their stay in hospital after pulmonary embolectomy (rib resection and drainage of lung abscess in one, and cholecystostomy in the other).

Six patients were discharged in good condition,

TABLE 1.—*Postoperative Status and Results in Eight Patients*

Patient	*Age*	*Sex*	*Recent Clinical History*	*Degree of Obstruction In Pulmonary Angiography*	*Operative Record*	*Result*
1.	44	M	Double coronary bypass. Chest pain and cardiac arrest on 8th postoperative day.	Angiography not performed.	1. Small amount of thrombus from LPA. 2. Thrombectomy of vein grafts.	Death during operation (autopsy was done).
2.	53	M	Single coronary graft. Pulmonary emboli on 10th postoperative day and shock.	40 to 50 percent	1. Large clot from LPA. 2. Operation for lung abscess two months after embolectomy.	Good
3.	67	M	Double coronary bypass. Severe chest pain on 14th postoperative day and shock.	Angiography not performed.	Long piece of clot from RPA.	Death during operation (autopsy not done).
4.	63	M	Single coronary bypass. Pulmonary emboli on 7th postoperative day.	50 percent	Large clot from LPA.	Good
5.	62	M	Patient in senile dementia, pulmonary embolism occurred.	>50 percent	Multiple clots from both sides.	Good. Sent to nursing home.
6.	46	F	Abdominal lipectomy and operation for vaginal suspension. Syncope on 10th postoperative day.	>50 percent*	Clots from both sides.	Good
7.	69	F	Patient with pacemaker, and cholecystitis in hypotension.	50 percent	1. Clot from RPA. 2. Cholecystostomy five days after embolectomy. 3. Tracheostomy.	Good
8.	64	F	Laporatomy for small bowel obstruction. Pulmonary emboli on 15th postoperative day.	>50 percent*	Saddle embolus.	Good

LPA = left pulmonary artery RPA = right pulmonary artery

*See Figures 1 and 2.

one of them being sent to a nursing home because he was unable to take care of himself because of senile dementia.

Necropsy Studies

Permission for autopsy could be obtained in only one of the patients who died during operation (case 1). Necropsy findings in this case showed thrombosis of coronary bypass grafts and thrombotic pulmonary embolus in the left lower lobe. Aorta and coronary arteries were reported to be hypoplastic and it was concluded that vein grafts were occluded mechanically due to the very small diameter of the coronary arteries (less than 2 mm) and poor distal runoff. In this patient there was no other medical cause (such as hypercoagulability) to explain the thrombosis of vein grafts.

Discussion

Pulmonary embolism occurs commonly in patients with a history of previous operation or chronic illness, in postpartum state or, rarely, in women taking oral contraceptives.[8] Evidence of thrombosis in the lower extremities and pelvic veins is not always a concomitant finding and has been observed in only one of our cases. Massive pulmonary embolism occluding 50 percent or more of the pulmonary arterial tree usually leads to clinical features of shock with a sudden severe reduction in cardiac output, acute right heart failure and disturbance of pulmonary ventilation and perfusion.[8] In rare instances it may also cause paradoxical systemic arterial embolism in patients with a patent foramen ovale or atrial septal defect as a result of increase in right atrial pressure and right-to-left shunt.[9,10] In unilateral pulmonary embolism cardiorespiratory difficulties may be augmented by pronounced spasm in the uninvolved pulmonary artery.[11] Development of cor pulmonale among patients surviving massive pulmonary embolism without embolectomy is extremely uncommon due to the rapid resolution of pulmonary thrombi under appropriate medical and prophylactic therapy.[12,13]

Prophylaxis of pulmonary embolism after coronary artery bypass surgical procedures deserves special mention. In all patients in whom coronary artery bypass operations are done, we carry out anticoagulation with warfarin sodium during the early postoperative period starting on the day chest tubes are pulled out (second postoperative day) and maintain administration of warfarin sodium until the day of discharge (usually the tenth postoperative day). To date we have observed significant pulmonary embolism needing embolectomy in only four of 2,000 patients in whom coronary artery bypass operations have been done. In a group of 100 patients we have not used any anticoagulation during the postoperative period to assess the importance of postoperative anticoagulation; in three of these there was significant pulmonary embolism needing embolectomy (cases 1, 2 and 4). In all other cases we used routine postoperative anticoagulation and found only one significant episode of pulmonary embolism (case 3). The rate of pulmonary embolism in these two groups of patients shows the importance of short-term postoperative anticoagulation in the prophylaxis of postoperative pulmonary embolism after coronary artery bypass operations.

The clinical diagnosis of pulmonary embolism cannot always easily be made because of such factors as frequency of sudden death, serious underlying diseases and erroneous diagnoses (for example, acute coronary occlusion); these are the most important causes limiting the number of patients who can be salvaged by embolectomy.

Although the diagnosis can be confirmed only by angiography, it may not be possible to carry out pulmonary angiography in some emergency cases, where the diagnosis must be based on history, physical signs, electrocardiographic findings and x-ray films of the chest,[16] as happened in two of our cases. Some surgical groups have advised the institution of an immediate femoral vein to femoral artery bedside bypass under local anesthesia in critically ill patients, and even in cases of cardiac arrest requiring resuscitation, before the transfer of the patients to the radiology department for pulmonary angiography.[6,17]

Acute pulmonary embolism can be treated by medical and surgical methods. Heparin is the most widely used drug for this purpose, and some favorable results have also been reported with the use of thrombolytic agents such as streptokinase.[8,18] Femoro-femoral membrane oxygenator support can be used in selected cases in addition to medical or surgical therapy.[19] Prophylactic methods like ligation or plication of inferior vena cava and insertion of umbrella filters are usually added in cases of continuous predisposition to venous thromboembolism leading to recurrent episodes of pulmonary embolism or when anticoagulation is contraindicated.[15] Fe-

moral vein ligation can be done under local anesthesia as a prophylactic measure in patients who are inappropriate candidates for general anesthesia.[15] We did not carry out any prophylactic surgical procedures such as ligation or plication of the inferior vena cava in addition to pulmonary embolectomy because we believe that adequate postoperative anticoagulation after mechanical removal of blood clots from the pulmonary arterial tree is sufficient for the treatment of patients in whom significant pulmonary embolism occurs for the first time without any previous recurrent embolic episodes.

The definitive surgical treatment for pulmonary embolism is pulmonary embolectomy, and the role of the procedure in the treatment of this pathologic condition still requires a clearer definition. It has been pointed out that patients with massive pulmonary embolism who are normotensive or whose hypotension is responsive to vasopressors do not usually need embolectomy and can be treated by medical and prophylactic measures only.[11,12,15,20] The common point of view in most publications on this topic is that pulmonary embolectomy should be reserved for patients with massive embolism occluding more than 50 percent of the pulmonary arterial tree accompanied by clinical shock.[7,15,21] We also agree with this indication, but we want to add one more point regarding the degree of obstruction in the pulmonary arterial tree. Our experience showed that pulmonary artery obstruction greater than 50 percent should not be a rigid criterion for pulmonary embolectomy because patients with less obstruction in the pulmonary arterial tree (less than 50 percent) are also sometimes candidates for embolectomy if they are in a clinical state of shock not responding to vasopressors.

Mortality after pulmonary embolectomy usually varies between 40 and 60 percent in most of the published reports,[15] although more favorable figures (23 percent) have been reported by some authors.[7,8] A history of cardiac arrest carries the poorest postoperative prognosis,[8,16] as also noted in our series.

Estimation of late mortality after pulmonary embolectomy is difficult unless necropsy can be done because patients may later die of other underlying diseases.

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Refer to: St. Geme JW Jr: Seminars in virology—A biological perspective of slow virus infection and chronic disease. West J Med 128:382-389, May 1978

A Biological Perspective of Slow Virus Infection and Chronic Disease

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Sequential events characterize the interaction of viruses with parenchymal cells, and acute lytic infections of tissues and organs have broad biological attributes. A knowledge of these permits a keener understanding of persistent, intermittent *herpesvirus infections and* persistent, continuous *respiratory virus infections. In addition to unique biochemical mechanisms which may permit the latter chronic infections to evolve, the roles of defective and mutant strains of virus, viral interference, and the genetic, developmental and immunological expressions of the host are of considerable and provocative importance.*

The traditional view of viral infections embraces a broad spectrum of acute pathological and inflammatory events. The relationship of measles virus to subacute sclerosing panencephalitis, the elucidation of the latency of herpes simplex virus, and the slow unmasking of the pathogenesis of multiple sclerosis have illustrated the subtle elements of persistent viral infections of the human being. These chronic neurological diseases have provided the opportunity and stimulus for sharp dissection of the biological and biochemical processes which embellish the logical link of viral infections to other forms of chronic human illness.

ONE OF THE most exciting periods of modern virology has evolved during the past several years. Suspected for a long time, the pathogenic relationship of human viruses to chronic illness is beginning to assume plausible and provocative attributes. The mystery of viral persistence, altered cellular physiology and immunological control mechanisms is being solved by careful biological research and extensive, multidisciplinary epidemiological studies.

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Presented in part at the National Pediatric Conference Honoring the Contributions of John A. Anderson to the Pediatric World, University of Minnesota Medical School, June 16-17, 1977, Minneapolis.

Submitted, revised, November 4, 1977.

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Host Cell-Virus Interaction and Cytoanatomical Events

It is important to know how virus particles interact with a mammalian cell. Mature particles attach to receptors on the cell surface where the early phases of uncoating of the viral capsid (protein coat) and penetration ensue. For many of the human viruses which are suspected to be causes of chronic diseases, the surface of the virion and the surface of the cell fuse and only

ABBREVIATIONS USED IN TEXT

CMV = cytomegalovirus
DNA = deoxyribonucleic acid
EBV = Epstein-Barr virus
HSV = herpes simplex virus
RNA = ribonucleic acid
SSPE = subacute sclerosing panencephalitis
T-cells = thymus-derived lymphocytes
ts = temperature-sensitive
VSV = vesicular stomatitis virus
VZV = varicella-zoster virus

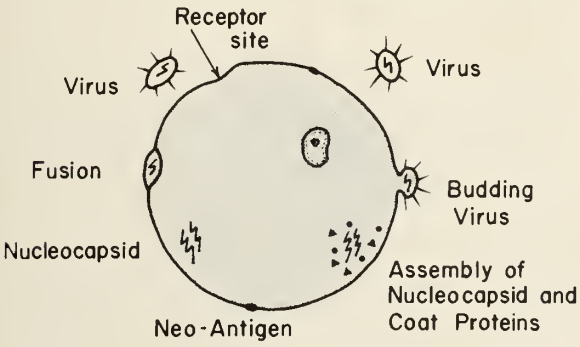

Figure 1.—Interaction between virus and host cell, including: the early phases of exposure, attachment, fusion-penetration and eclipse; the subsequent synthesis of new viral cytoplasmic components and cell surface antigens; and the final enveloping, budding and release of progeny virions.

the genetic material of the virion, the nucleocapsid, actually enters the cell. Implemented by viral and cellular enzymes, the genetic material of the virus is transcribed and translated into new genome, enzymes and structural proteins sufficient for the assembly of progeny virus particles. These subtle and complicated biochemical events transpire quickly during a period of eclipse when viral particles or subunits can no longer be detected by ultrastructural analysis. As new viral components are synthesized, they aggregate beneath the plasma membrane of the host cell, become packaged into new virions, are enveloped by host membranes and, finally, are budded off the surface of the cell into the extracellular environment (see Figure 1). In the course of these virus-induced intracellular events, the plasma membrane may be altered slightly by the substitution of glycoprotein units of the viral coat as new antigenic determinants on the cell surface.

The Biology of Acute Viral Infection

Extending the background of understanding, it is important to note the impact of an acute, lytic viral infection upon the host cell. The diversion

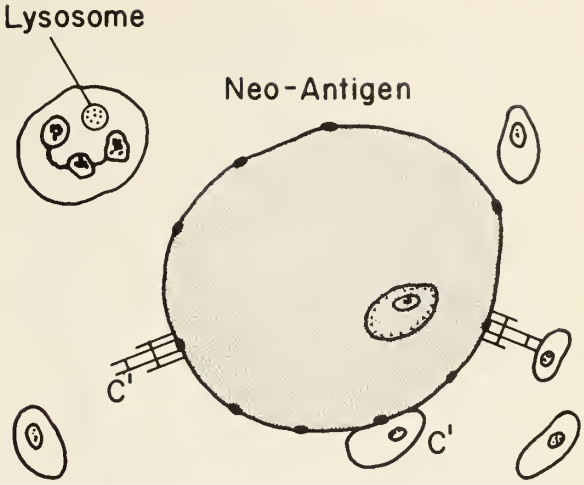

Figure 2.—Immunological and inflammatory recognition of an infected cell with viral-programmed surface antigenic determinants and the immunocytopatholytic events mediated by T-lymphocytes, monocytes, antibody-dependent killer mononuclear cells and the interaction of complement (C′) with specific antibody and immunocytes. Polymorphonuclear leukocytes, containing potent lysosomal enzymes and phagocytic function, execute a final inflammatory dissolution of damaged cell populations.

of biochemical processes to the production of new viral particles may be accompanied by a shutting-off of intrinsic cellular deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein synthesis. The appearance of new antigenic determinants on the cell surface permits immunological recognition by specific viral antibody, thymus-derived lymphocytes (T-cells) and complement (see Figure 2). Their aggregation about the infected cell produces immunopathic cytolysis and the elimination of damaged, virus-releasing cells. Polymorphonuclear leukocytes and mononuclear macrophages also participate in this inflammatory pathologic process. These cells are attracted to the scene by chemotactic immunoproteins and complement, and contribute to the final dissolution of host cells bearing persistent virions, viral genome or nucleocapsid structures.

These processes explain the characteristic histopathology and pathophysiology of acute viral infections, including: (1) interstitial pneumonia, surfactant-depleted atelectasis, ventilation-perfusion dysequilibrium and hypoxia; (2) intraluminal gastrointestinal solute and water loss and transient malabsorption of fat and carbohydrate; (3) vasculopathic cerebral edema, meningeal inflammation, cortical and cord neuronal dysfunction and paresis; (4) hepatocytic necrosis and edematous canalicular obstruction, and (5) the

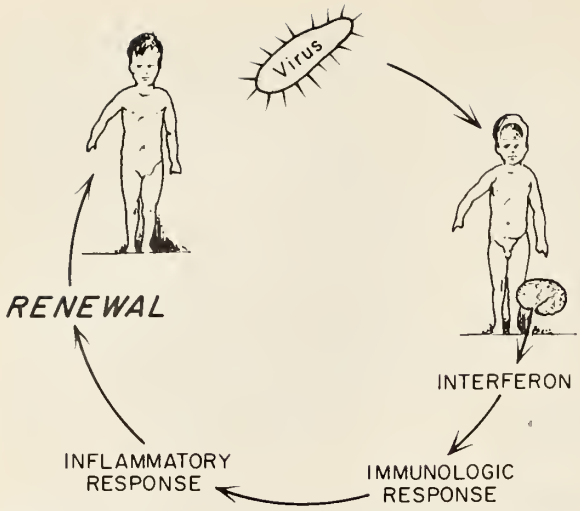

Figure 3.—Sequence of acute viral infection; altered histopathology and pathophysiology; the elaboration of regulatory antiviral protein, cellular and humoral immunity, and inflammation; and the ultimate restoration of normal structure and function.

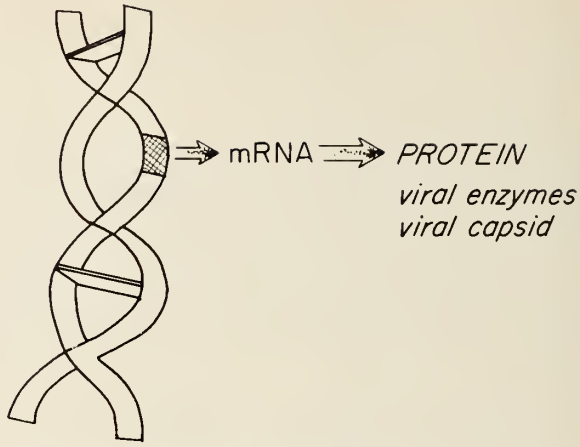

Figure 4.—Persistent, intermittent infection with the integration of viral DNA (hatched) into host cell DNA and the subsequent transcription of messenger RNA (mRNA) for the synthesis of essential enzymes and coat (capsid) proteins for new virions.

epidermal necrosis and perivascular inflammation which characterize the vesicular and morbilliform exanthems.

With acute viral infection there exists ample opportunity for restoration of damaged and destroyed cells within an organ. As antibody production and T-cell mediated cellular immunity unfold and are embellished by inflammation and the capability of host cells to synthesize interferon, an important regulator of subsequent viral replication, the burden of virus subsides and cellular renewal begins (see Figure 3). In most instances, patients are left without any anatomical or physiological residue.

Persistent, Intermittent Viral Infection

The herpesviruses provide a classic example of chronic viral infection. This family of viruses, herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), are apparently able to position their viral DNA either into the DNA of the host cell or very close to it. This "integration" is important because all of these viruses produce relapsing, reactivation forms of illness, possibly even EBV.

The clearest understanding of this relationship involves HSV. HSV DNA may be "integrated" as latent genetic material in the nucleus of ganglionic neurons (see Figure 4). The experiments of Stevens and his colleagues[1-3] have elucidated this exciting biology in an elegant fashion. These workers have suggested that specific HSV neutralizing antibody may hold the genome in check,[4] although one suspects that cell-mediated immunity is a more critical determinant of control of HSV reactivation. When one of the many events which permit derepression of this viral genome occurs, the full-scale production of mature HSV virions is triggered within the neuron and new viral particles flow down the axoplasm to the epidermal surface where they evoke the lytic alterations of a recurrent, vesicular eruption. The same biological process is likely operative for the pathogenesis of herpes zoster or shingles. CMV and EBV may remain latent in a similar manner in epithelial and lymphoid cells which, in contrast to neurons, are capable of division.

DNA-viruses, including the adenoviruses,[5] seem to be uniquely capable of establishing latency followed by intermittent episodes of reactivation, repetitive viral shedding and acute clinical illness.

Persistent, Continuous Viral Infection

Following a primary overt or subclinical infection, virus may persist in the host cell for prolonged periods of time. Paramyxoviruses and arthropod-borne viruses (arboviruses) loom as the most likely candidates for establishing chronic infection in human tissues, particularly in cells which do not undergo constant renewal. A compelling example is the devastating disease subacute sclerosing panencephalitis (SSPE), in which measles virus nucleocapsid structures are found to cortical neurons and glial cells.[6] Although ultrastructural studies have not confirmed the presence of viral components, the vast source of

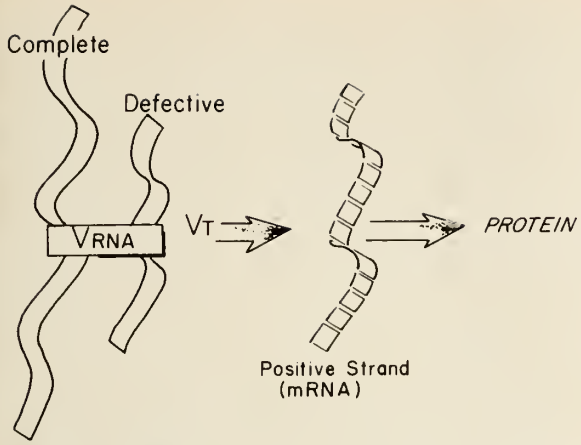

Figure 5.—Persistent, continuous infection with the presence of viral transcriptase (VT) enzyme which permits negative strand viral RNA (VRNA), the genome of myxoviruses and paramyxoviruses, to serve as the template for the RNA to RNA copying of positive strand viral messenger RNA (mRNA) and ultimate synthesis of viral proteins. Defective viruses compete with complete viruses for the critical use of VT and thus interfere with the replication process of complete viruses.

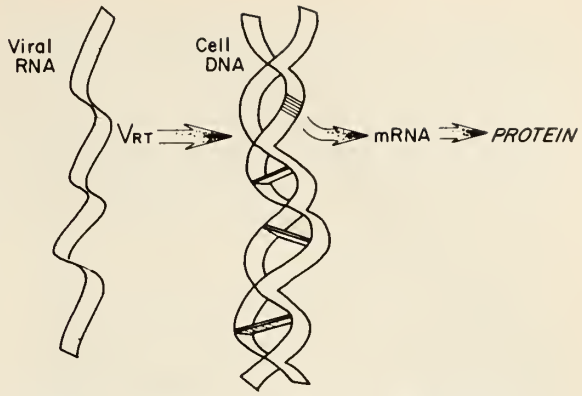

Figure 6.—Persistent, continuous infection with the presence of viral reverse transcriptase (VRT) enzyme which permits negative strand viral RNA to serve as the template for the reverse copying of an RNA to DNA segment which may be integrated into the DNA of the host cell.

serological and epidemiological data suggests that measles virus may be linked to multiple sclerosis, viral genome being reservoired in astrocytes and oligodendroglial cells which provide axonic myelin sheaths.

In contrast to the DNA-virus infections discussed above, the infections produced by these RNA-viruses may be constant, simmering processes.

Biochemical Aspects

Paramyxovirus RNA genome can be transcribed to produce messenger RNA molecules which code for new viral genome, enzymes and structural proteins. These events occur because of the inclusion of transcribing enzyme, RNA transcriptase, into the structural proteins of the mature virion (see Figure 5). It is conceivable that a virus so smartly prepared for its biochemical mission may produce new viral RNA within a cell which can persist undisturbed for many years. Persistent viral RNA may be capable of coding for special viral protein which, while failing to complete the process of viral replication, can alter either cellular function or surface membranes.

However, very recently a more plausible biochemical explanation for the persistence of paramyxoviruses has evolved. Similar to the biochemical function of mammalian and perhaps human RNA tumor viruses, several paramyxoviruses have been discovered to be capable of producing transfection[7] (see Figure 6). Transfection is a process by which viral RNA may transcribe or produce a DNA homologue which in turn may be approximated to the host cell DNA in anatomical location and, most important, in concurrent biological expression. The RNA tumor viruses possess a critically important enzyme as part of their constitutive structure which carries out this extraordinary biochemical annexation of fundamental host cell processes. The enzyme is aptly named reverse transcriptase, indicating the copying of DNA from RNA, in contrast to the RNA to RNA copying which is mediated by the aforementioned viral transcriptase. Indirect evidence suggests that under certain conditions respiratory syncytial virus, measles virus, rubella virus, Newcastle disease virus and visna virus possess reverse transcriptase enzyme.[7-9] Although respiratory syncytial virus and Newcastle disease virus have not been implicated in chronic disease processes, measles virus has been clearly linked to SSPE, possibly linked to multiple sclerosis, and evidence has been advanced recently to suggest that DNA copy of measles virus RNA is integrated into the host cell DNA of patients with systemic lupus erythematosus.[8] Furthermore, rubella virus has been isolated from the brain of a child with chronic panencephalitis and linked to chronic encephalopathy in other patients.[10]

Another explanation for the persistence of viral genome within the cell implicates a biochemical peculiarity of the host cell itself. Cellular protease enzymes cleave away some of the viral nucleocapsid, rigidifying nucleocapsid structure to such an extent that the nucleocapsid may not be able

to fold into the enveloping configuration of the viral protein coat and the lipids of the cellular plasma membrane.[11,12] The protease altered viral nucleocapsid may also lose ability to home into the budding site on the plasma membrane where the final assortment and packaging of viral components occur before completion of infection and release from the cells.

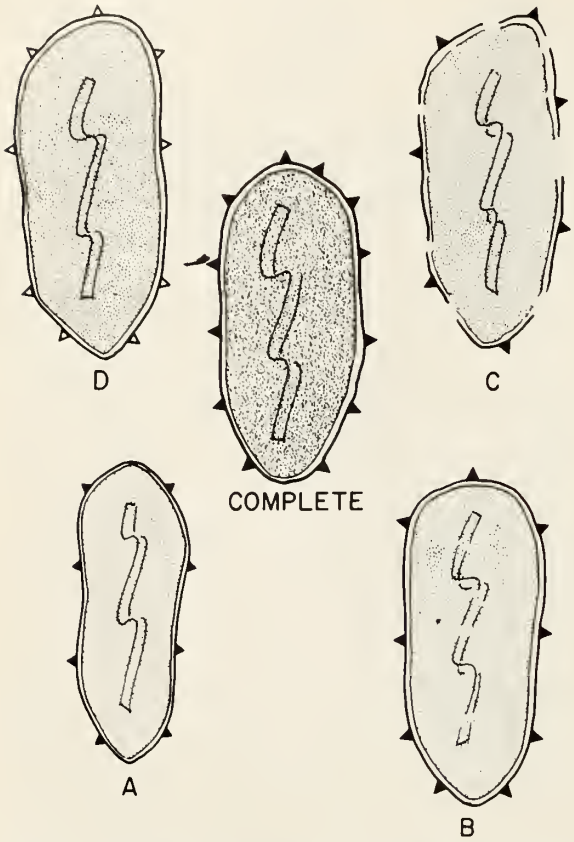

Figure 7.—Defective viruses may be smaller **(A)** than complete viruses, may contain genomic deletions **(B)**, may be encapsidated by unstable structural coat proteins **(C)**, or possess fewer external coat protein components **(D)**.

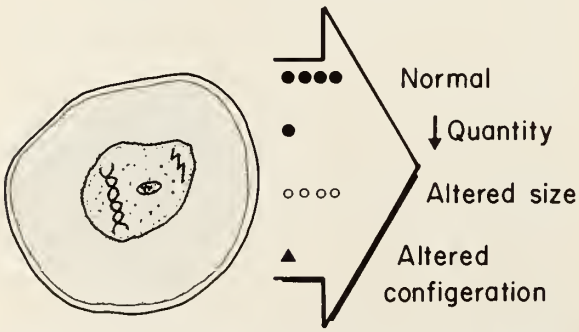

Figure 8.—Biochemical and physiological disturbance of the synthesis of protein product by a parenchymal cell with persistent, continuous infection.

Defective Viruses

In addition to these biochemical explanations for the persistence of viruses in human tissues, there exists the provocative biological phenomenon of defective viral particles and the expression of viral interference (see Figure 7). The quantitative anatomy of defective viruses is difficult to analyze. Precise biophysical evaluation of vesicular stomatitis virus (VSV), a virus of little human importance, indicates that defective VSV is smaller than complete mature VSV.[13] The same seems to be true for parainfluenza virus type 1 and possibly measles virus.[14,15] Other defective viruses, while of the same total size as standard complete virions, possess small deletions of their genome which impair their biochemical function during the early phases of viral replication. Defective Sindbis virus has a small lesion in the viral RNA which results in the transcription of smaller messenger RNA molecules with the ensuing production of fewer or unstable structural proteins for the viral coat.[16] Defective influenza virus has a decreased amount of transcriptase enzyme and synthesizes in the course of infection a decreased amount of the longer RNA segments which constitute the genome of virus.[17] Defective virions compete more successfully with standard virions for viral RNA polymerase enzymes and effectively turn off the reproduction of standard virus particles.[13,18] Defective viruses do not consummate their own replication very efficiently and they persist within cells without the provocation of the biochemical and immunological mechanisms which can destroy virus-producing cells. As an example, standard reovirus produces an acute encephalitis in mice, while defective reovirus produces a slowly evolving chronic hydrocephalus.[19] Perhaps, sufficient viral genome persists in the host cells to produce some regulatory proteins. If certain of these viral-coded proteins perturb the normal biochemical mechanism of parenchymal tissues, physiological malfunction of an organ might result. An example might be a diminished or abnormal protein product by a critical organ, such as insulin or thyroxin (see Figure 8).

Immunopathologic Aspects

One of the prevailing pathogenetic theorems for multiple sclerosis consists of direct viral involvement of oligodendroglial cells and the consequent impairment of myelin production.[20] A similar demyelinating process may occur if virus

disturbs the normal biological function of neurons with subsequent axon injury, followed ultimately and secondarily by demyelination. Extending the example of multiple sclerosis, immunological phenomenon may be overlaid on the initial biochemical disturbance within glial cells. If transfecting or defective viral nucleocapsids can persist within parenchymal cells, they may possess enough biosynthetic capability to alter the cell surface with new glycoprotein antigenic determinants. Low intensity immunoreactivity of the host may produce a more chronic autoimmune form of histopathology rather than acute immunopathic destruction of infected cells. This immunopathological process can escalate multiple sclerosis with inflammatory bursts and relapses. Immunopathic elements may also amplify the relentless course of chronic cerebral dysfunction in SSPE.[6] Thyroiditis, diabetes mellitus and the cardiomyopathies may represent illnesses where persistent forms of viral infection produce a primary direct biochemical and physiological hit on the host cell, followed by a secondary, chronic immunopathological inflammatory process. There is ample evidence for circulating and tissue-bound immunoproteins and T-cell lymphoid responses in both experimental and human thyroid and myocardial disease.[21] Although the relationship of group B coxsackie viruses to juvenile diabetes mellitus in humans remains equivocal, despite compelling evidence in experimental animals that enteroviruses can produce diabetes, the relationship of juvenile diabetes mellitus to mumps virus, another paramyxovirus, may prove to be real.[22-25]

Attenuated and Mutant Viruses

In closing discussion of the biochemical and biological attributes of persistent viruses, a comment should be made about attenuated viruses and temperature-sensitive (ts) mutants. Attenuated poliovirus, a ts mutant, consists of defective virions.[26] Mutant strains of measles virus, produced *in vitro* by chemical agents, can evoke modified infections in experimental animals, including a progressive form of hydrocephalus.[27] Ts mutants of vsv persist in the brains of mice, occasionally producing mild pathological changes in contrast to the fulminant disease of standard vsv particles.[28] Mutagenic chemicals have permitted the recovery of ts mutants of other paramyxoviruses, which offer for vaccine development the attractive aspect of replication only at the lower body temperature of the upper respiratory tract. Unfortunately, some of these ts mutants also possess genomic deletions which render these particles partially defective and potentially capable of persistence. To date, a relationship of attenuated human vaccine viruses with persistence and chronic disease has not been documented.

Ts mutants of parainfluenza virus type 1 are unable to direct the synthesis of a pivotal coat protein, the hemagglutinin-neuraminidase glycopeptide. While virus can replicate in host cells, the usual cytolysis does not occur, offering substantial concern about the possibility of persistence.[29] Although wild strains of Newcastle disease virus possess transcriptase enzyme, only mutant strains possess the reverse transcriptase so important for the phenomenon of transfection.[9] Measles virus ts mutants induce infection with the accumulation of viral antigen in the nucleus and cytoplasm of host cells but fail to code for effective coat protein function at the plasma membrane.[30]

The Host

The suggestion has already been made that the host cell may share some of the blame for chronic, persistent viral infections. Certain tissues and organs produce a greater population of defective particles than others and in the case of some experimental animal models this phenomenon is closely regulated by heredity.[31-33] Certain cells permit the expression of the phenomenon of viral interference more extensively.[34]

The immunological response of the intact host may be of critical importance in the pathogenesis of a chronic viral infection. Probing for a genetic linkage to susceptibility and immunological response, the haplotypes HLA-A_3, HLA-B_7, HLA-DW_2, and the new B group 4 have been found more frequently in patients with multiple sclerosis.[35] Although the data are inconsistent, multiple sclerosis patients may have diminished expression of cell-mediated immunity to measles virus and perhaps other viruses, despite the fact that T-lymphoid cells from these patients react more vigorously with measles virus-infected cells *in vitro*.[36-38] If cellular immunosuppression proves to be true and important, an explanation may be sought from the observation that measles virus replicates in mononuclear cells and could diminish the immunological function of these lymphoid cells.[39]

While it is logical to conclude that a specifically immunosuppressed host may encumber persistent viral infection, the permissive relationship of specific antibody to persistent infection is even more provocative. Constant low levels of humoral measles virus antibody can polarize or "cap" viral antigenic determinants on the cell surface and strip away the antigen, precluding the total dissolution of the virus-producing cell by immune complex or T-cell mediated immunocytolysis.[40] In this way, virus, possibly defective, maintains effective sanctuary. Interestingly, persistently infected cells produce much less plasma membrane measles virus antigen than cells infected with wild measles virus.[41]

Cells infected with defective virus are less able to envelop and release new virions, and so they are less susceptible to the removal of infected cells by immunocytolysis. More potent antibody to the most integral structural components of the viral capsid and envelope may be missing in individual humans or animals with defective mutant virus infection, simply because viral antigens are not delivered to the surface of the cell where the immunopoietic and immunocellular components of the host may recognize and respond.[42] In slow, persistent visna virus "transfection" of the sheep choroid plexus, only 0.1 percent of the cells containing reversely transcribed viral DNA produce complete virus and new viral proteins.[43]

It is important to realize, as has been suggested for the chronic, intermittent infections of the herpesviruses, that vigorous antibody response, and perhaps cellular immunity as well, may make the virus "take a dive" and become more intricately integrated into the structural and biochemical elements of the cell. In this regard, intracerebral infection of rhesus monkeys with human SSPE measles virus produces an acute, fatal, degenerative, relatively noninflammatory encephalopathy in nonimmune primates, whereas in naturally immune animals chronic, progressive encephalitis develops with elevated cerebrospinal fluid antibody, glial cell proliferation and perivascular inflammation.[44]

The age of the host is of considerable importance. Defective-interfering particles are elaborated more extensively by infant mice infected with vesicular stomatitis and rabies viruses.[45] Neonatal hamsters seem to be more susceptible to the chronicity of experimental measles virus infection than older animals.[46] There is intriguing epidemiological evidence from the Middle East suggesting that SSPE occurs more often in children in whom primary measles virus infection developed when they were infants rather than during later childhood.[47] Increased multiplication of measles virus has been noted in the mononuclear cells of newborn humans, presumed to result from the heightened DNA and RNA metabolism of infant cells.[39] Measles virus may gain access to more remote sites such as the central nervous system by hematogenous transport in leukocytes.

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Smoking, Alcohol and Cancer of the Larynx

LARYNGEAL CANCER seems to be related to consumption of alcohol. Even when we analyze the data from studies of laryngeal cancer and control for the amount of excess smoking that heavy drinkers engage in, we still see an increase in risk in cancer of the larynx due to alcohol consumption. It seems from recent studies, too, that the increases in risk for cancer of the larynx from tobacco smoke and from alcohol seem to be synergistic—they interact—so that a certain amount of risk from smoking is not just added to a certain amount of risk from alcohol. The increase in risk is much more than you would get just from summing up the individual risks conferred by each separate factor. So there seems to be a synergy involved in increasing larynx cancer risk.

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Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 10, No. 12, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Johnston DG: Blood transfusion: Use and abuse of blood components. West J Med 128:390-398, May 1978

Blood Transfusion: Use and Abuse of Blood Components

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Transfusion of whole blood and some blood components may result in serious or fatal complications, among which hepatitis is most frequent (20,000 to 30,000 cases and 3,000 deaths a year). Although hepatitis B virus (HB Ag) sometimes is implicated in posttransfusion hepatitis, non-A non-B virus(es) (hepatitis "C" virus) probably accounts for most posttransfusion hepatitis.

Half of all blood transfusions may be unnecessary.

Responsible transfusion practice requires use of appropriate blood components for which there is adequate justification. Transfusion of red blood cells should be given as packed cells in most instances and whole blood should seldom be used.

TRANSFUSION THERAPY for anemia should be considered a "last resort" because of the many dangers to the recipient. There are few injectable agents used in medicine that carry so many and such severe hazards for a patient.

Several years ago it was estimated that nearly 3,000 deaths were occurring annually in the United States as a result of transfusion of 3.5 million patients.[1] The incidence of unnecessary transfusion was then estimated, as it is today, to be approximately 50 percent of all transfusions.[2] In today's courts of law, approximately 1,000 of those deaths might have been judged the result of involuntary manslaughter.[3] It has been recently estimated that more than 8 million units of blood and blood products are now being used in this country each year[4] with 20,000 to 30,000 cases of posttransfusion hepatitis and an annual death rate of 3,000 people from posttransfusion hepatitis alone.[5]

Complications of blood transfusion (Table 1) are of many types and some are extremely dangerous to the life of patients and, incidentally, to the security of physicians. Table 2 lists the types of transfusion reactions encountered.[10]

Hepatitis occurs with greater frequency (0.3 percent to 0.8 percent)[11] than the other serious complications. Hepatitis carries a mortality rate of approximately 1 percent to 20 percent[11] and, although hepatitis B virus (HB Ag) has been implicated in posttransfusion disease, most posttransfusion hepatitis is due to hepatitis "C" virus (non-A non-B hepatitis virus).[12] Hepatitis A disease is usually less severe than that resulting from hepatitis B virus and residual severe liver disease and death are infrequent.[13] Although there is a test for hepatitis A antibody in serum (immune adherence test),[14] there is no practical test for hepatitis A virus in blood products[13] and cur-

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Submitted, revised, December 8, 1977.

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ABBREVIATIONS USED IN TEXT
ACD = citric acid, trisodium citrate, dextrose
ATP = adenosine triphosphate
CPD = citrate phosphate dextrose
2,3-DPG = 2,3-diphosphoglycerate

rent tests cannot detect all donors capable of transmitting hepatitis B positive hepatitis.[15] Donor services, after excluding commercial and hepatitis antigen positive donors, report a frequency of hepatitis of 3.7 cases per 1,000 units transfused, indicating that it is not yet possible to identify all donor carriers. Donors with hepatitis B antibodies should not be excluded because they offer some protection against the disease.[15]

Of volunteer donors, 0.1 percent to 0.4 percent are hepatitis B antigen carriers but the rate is much higher among commercial donors; 5 percent of drug addicts are thought to be carriers and the normal person who is infected with hepatitis B antigen rarely becomes a carrier. If he or she does, it is probably for life.[14]

Recent advances in hepatitis research include successful transmission of hepatitis caused by hepatitis B, hepatitis A and hepatitis "C" viruses to nonhuman primates. Development of tests for antibody has led to improved immune serum globulin for prevention of infections. Preparation of hepatitis B inactivated vaccine now under trial offers hope for control of hepatitis B disease. The safety, immunogenicity and protective effect are yet to be proved. The new problem is the recent recognition of a non-A non-B variety of virus (hepatitis "C" virus) caused hepatitis in patients receiving multiple transfusions.[14] This virus (or group of viruses) probably accounts for most cases of posttransfusion hepatitis. So, with all that has been accomplished in research and test developments, there is no way to insure that any unit of whole blood is free of hepatitis virus.

We physicians have an obligation to keep current with developments in transfusion therapy in order that we utilize the safest and most effective blood component in treating patients.

TABLE 1.—*Complications of Blood Transfusion*

Transfusion Reactions
Hepatitis
Sensitization
Infections:
- Brucellosis
- Syphilis
- Malaria
- Trypanosomiasis[6]
- Cytomegalic virus[7]
- Epstein-Barr virus[8]

Air embolism
Thrombophlebitis
Disseminated intravascular coagulation
Dilution thrombocytopenia
Potassium and/or ammonium toxicity
Pharmaceutical incompatibility with drugs taken by donor
Graft vs host reaction (donor lymphocytes vs recipient)[9]

Modern Transfusion Therapy Means Component Therapy

Component therapy not only allows achievement of a more effective therapeutic level of the needed blood fraction but it extends the available blood resource since each unit of whole blood can meet the needs of multiple recipients. The proper use of blood requires:[4]

TABLE 2.—*Transfusion Reactions*

Cause	*Symptoms*	*Frequency*	*Prognosis*
Allergy	Itching, urticaria, fever, bronchospasm, angioneurotic edema	Common	Good
Unknown (febrile)	Chills, malaise, fever, headache	Common	Good
Circulatory overload	Dyspnea, cough, hemoptysis, tachycardia	Rare	Good
Contaminated blood	Chills, fever, headache, backache, delirium, hematemesis, diarrhea	Rare	Serious
Red cell incompatibility	Chills, fever, headache, backache, hematuria, oliguria, jaundice	Moderate	Serious
Antibodies			
1. RhD in gamma fraction	Same	Rare	Good (delay in transfusion)
2. Penicillin	Same	Unusual	Good
Sensitivity to donor:			
Leukocytes	Chills, fever, malaise, headache, confusion	Common	Good
Platelets	Same	Rare	Good
Plasma	Same	Rare	Good

- Knowledge of pathophysiology of condition being treated.
- Identification of the specific deficiency needed by the patient.
- Choice of appropriate component for therapy.

Multiple hazards to the patient and attendant risks to physicians and hospitals will be reduced by elimination of unnecessary blood transfusion and by proper use of blood component therapy when blood transfusion is necessary.

The indications for blood transfusion are relatively few; the usual being to maintain or increase blood volume and also to improve or maintain oxygen carrying capacity, with the unusual being to replace toxic circulating blood or to enhance coagulation, or both.

In most instances, use of whole blood for volume maintenance would be limited to considerable acute blood loss and would require two or more units. It has been observed that acute blood losses of 1,000 to 1,500 ml of blood from previously normal adults can be compensated by use of plasma expanders if blood loss can be stopped.[16] Spontaneous reestablishment of hemoglobin begins soon after an acute bleed in most cases, the amount increasing 0.1 to 0.3 gram per dl per day.[17] There are prevalent misconceptions that may account for some abuse of transfusions. Some surgeons have expressed the view that healing will be more rapid if hemoglobin levels are maintained within the normal range. We are aware of no convincing evidence to support this belief. Some surgeons and anesthesiologists believe that a long operation is in itself an indication for whole blood transfusion; that all patients with symptoms of shock and blood loss need whole blood, and that it is unsafe for mildly anemic patients to undergo a major operation without preoperative transfusion to elevate the hemoglobin level. Many also believe themselves able to estimate operative blood loss accurately. These misconceptions account for unnecessary transfusion and risks to recipients.

One series of 100 patients with benign ulcers underwent elective partial gastrectomy for reasons other than recent severe hemorrhage. In only two was blood transfusion required during operation and in none afterward.[18] Dr. Crosby has indicated that, if volume of blood is normal, a hemoglobin level of 7 grams per dl is sufficient for tissue oxygenation in most surgical situations.[19] One well known surgeon of this area has stated that a patient with a hemoglobin concentration of 11 grams per dl before operation would usually be safer in donating a pint of blood than in receiving one.[20]

The use of plasma substitutes for volume maintenance does not receive the attention it deserves. Patients requiring only one or two units of blood should probably receive a plasma substitute.[16] It is desirable to exclude the plasma from the transfusion unit if possible because leukocytes and platelets form microaggregates in the donor plasma and their concentration increases with storage time. These microaggregates may become trapped in the recipient's pulmonary microcirculation and promote respiratory failure. Donor leukocytes may also activate cellular and humoral immune response in the recipient resulting in sensitization of an existing or subsequent organ transplant.[21]

The use of blood to improve oxygen carrying capacity in an anemic patient is complicated by the requirement to assess the needs of the patient. These needs for oxygen vary depending upon altitude, age and physical activities. It is helpful for physicians to be acquainted with the "normal" or "usual" hemoglobin levels for the various ages and activities of male and female patients in their own geographical area. For example, we have observed the usual hemoglobin level for young housewives at sea level to be between 10.5 and 13.5 grams per dl. In young men of similar age the range is from 12.5 to 16 grams per dl. In 633 "normal" women in Spokane, Washington, (elevation 2,000 feet) a mean hemoglobin level of 12.55 grams per dl was reported.[22]

In considering transfusion of whole blood or red cells, it is important to recognize that each unit (pint) will increase the hemoglobin level by only 1 to 1.5 grams per dl.[17]

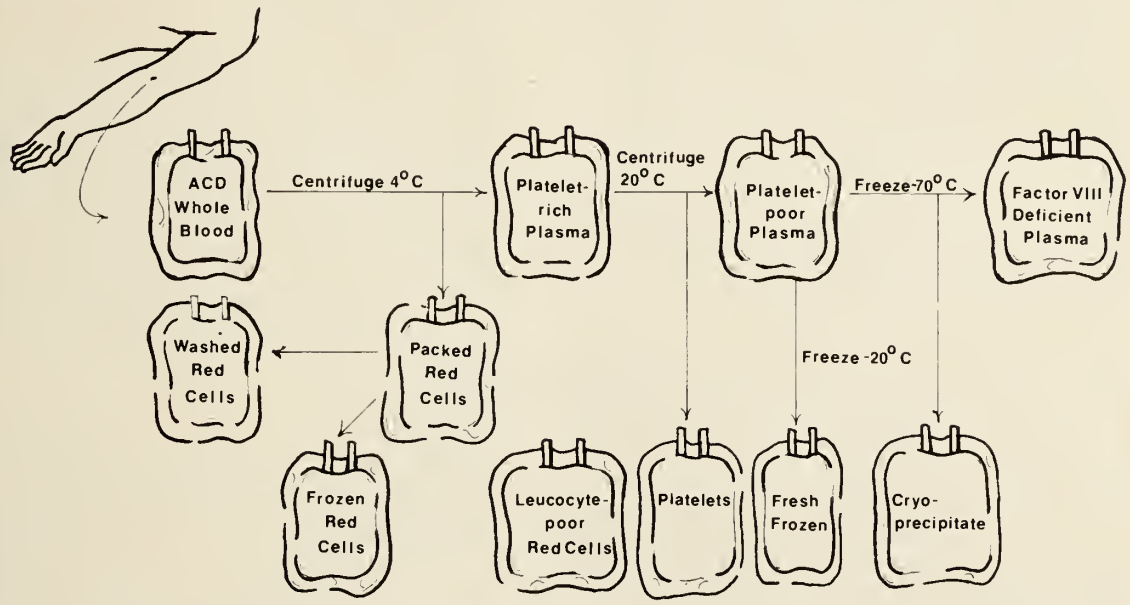
The merits of a single unit transfusion must be weighed against the many hazards to the recipient when he or she will have benefit of only a 5 percent to 10 percent increase in hemoglobin from the single unit.

Twelve years ago a review of this subject in a Southern California hospital showed that 47 percent of transfusions were single unit and that 80 percent of those were probably unnecessary. One year later, after several educational presentations on blood transfusion therapy, the single units had dropped to 42 percent of which 52 percent were probably unnecessary. In 1972 the single unit

transfusion rate was 21 percent, and 43 percent of these were deemed unnecessary. In 1974 single unit transfusions were 19 percent, and 30 percent of these were felt to have been unnecessary.[23]

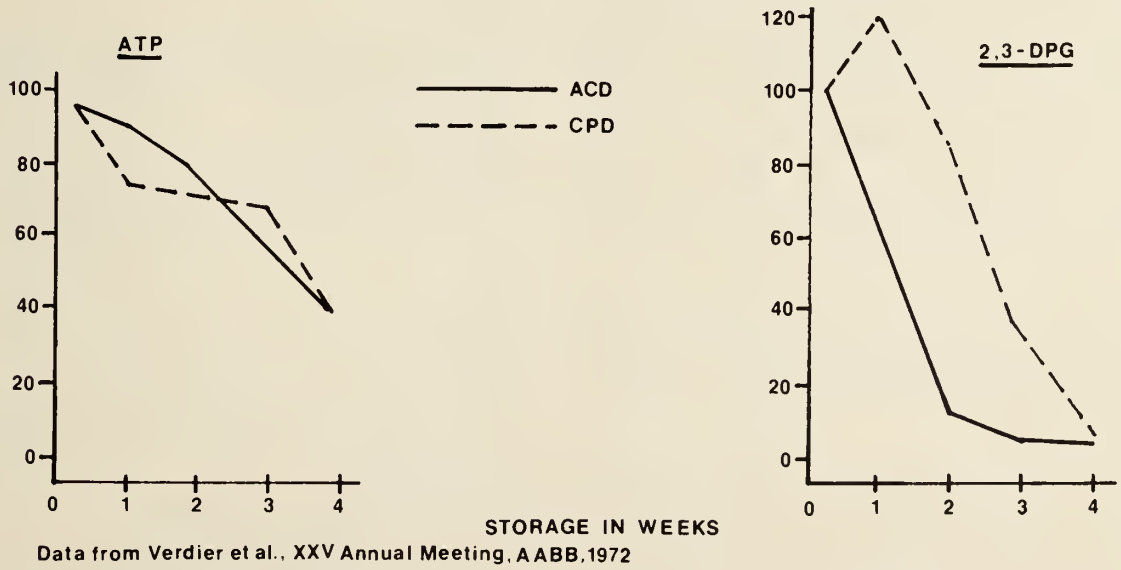
Improvements in transfusion practice are slow. Component therapy must be considered when we think of transfusion.

Most blood banks accept donors who have been screened by a physician who takes the blood pressure and pulse, and records the temperature. The patient must be of a certain age, and weight, and must have had a history of good health. (Criteria for donor selection are included in the Appendix.)



PRIMARY INDICATIONS	Anemia & Hypovolemia	Organ Transplants Patients	Anemia	Leucocyte Reactions	Thrombo-cytopenia	Multiple Factor Deficiency	Hemophilia A	Hemophilia B

Figure 1.—Scheme for component separation (Modified from Hinkes and Steffen[24])



Data from Verdier et al., XXV Annual Meeting, AABB, 1972

ACD = citric acid, trisodium citrate, dextrose
ATP = adenosine triphosphate
CPD = citrate phosphate dextrose
2, 3 DPG = 2, 3-diphosphoglycerate

Figure 2.—Effects of storage of whole blood in ACD and CPD solutions

The blood collected in citric acid, trisodium citrate, dextrose (ACD) solution may be processed for component therapy in a manner illustrated by Figure 1.[24]

Such separation as indicated in Figure 1 provides convenience, relatively low cost, and safety. When the blood is stored in the anticoagulant solution, erythrocytes will undergo chemical and physical changes which have been referred to as *storage lesion.*[25] They lose their capacity to deliver oxygen efficiently to the tissues and ultimately their capacity to survive for more than a few minutes in the circulation of the recipient. The rate at which the storage lesion occurs is a function of the preservative and condition of storage. The preservative should allow the red cells to survive after transfusion and to retain the ability to release oxygen into the tissues. Two substances in the red cell are important in oxygen release: adenosine triphosphate (ATP) which regulates red cell viability and 2,3-diphosphoglycerate (2,3-DPG) which determines oxygen release.[25] Other than freezing, there are only two practical red cell preservatives used at this time; one is the ACD solution developed in the early 1940's (during World War II) by Drs. Ross and Finch,[26] and the newer citrate phosphate dextrose (CPD) solution which is associated with a tendency of platelets to clump.

ATP, concerned with viability of red cells, appears to be about the same for both preservatives (Figure 2). The level of 2,3-DPG concerned with oxygen release, however, remains in greater concentration for a longer period with CPD. Consequently, the oxygen delivering capacity is much higher with CPD. The importance of this illustration relates to the requirements of patients. If a patient requires blood with a high immediate oxygen-carrying capacity, it should probably not be more than a week old if stored in ACD solution or two weeks in CPD solution.

It is interesting that the release capacity of transfused cells will return to normal within a day or so after transfusion. Therefore, the use of blood that has been stored for longer periods is probably harmful only when given in large amounts over a short period.[25]

There are many difficulties for transfusion services in provision for blood requirements today. There is great demand for these products and, if we continue to use whole blood for patients who could equally well be treated with components, there simply will not be enough blood

TABLE 3.—*Packed Red Cell Transfusions*

	1972 (Percent)	*1974 (Percent)*
Single unit	25	84
Double unit	33	93
Triple unit	33	84
Four or more*	28	52
All transfusions	30	60

*Includes open heart cases.

TABLE 4.—*Advantages of Packed Red Blood Cells*

- Per unit volume transfused, hemoglobin replacement with packed red blood cells is twice that with whole blood.
- Decreased likelihood of circulatory overload.
- Decreased incidence of nonhemolytic transfusion reactions.
- (?) Decreased incidence of serum hepatitis.
- Safe use of common bloods—O and A in place of B and AB.
- Bonuses:
  - Platelets
  - Leukocytes
  - Cryoprecipitate
  - Factor VIII—depleted fresh frozen plasma
  - Remaining plasma for fractionation into albumin and gamma globulin

TABLE 5.—*Indications for Red Cell Therapy*

Packed red blood cells (80 percent to 90 percent of *all* transfusions)
- Moderate blood loss.
- Chronic anemia not likely to respond to medical therapy.

Whole bank blood
- Moderate to massive blood loss equaling one-half to one times total blood volume; should be alternated with fresh whole blood when loss exceeds total blood volume.
- Exchange transfusion.
- Open heart surgical operation.
- Burns accompanied by anemia and hypoproteinemia.

Fresh whole blood (within 24 hours of collection)
- Probably no good indication if specific components are available.

Frozen blood
- Rare blood types (specific antibody to "public" antigen).
- Patient with multiple red blood cell antibodies.
- Candidates for organ transplantation, (not always helpful since graft survival is sometimes better in patients having received whole blood transfusions).[30]
- Blood shortages.
- Autotransfusion.
- Paroxysmal nocturnal hemoglobinurea.

Packed red blood cells—buffy coat poor
- Patient with severe transfusion reactions due to platelet, leukocyte, or plasma protein antibodies.

Washed red blood cells
- Paroxysmal nocturnal hemoglobinurea.

to go around. There is little justifiable reason today to transfuse a patient with whole blood to improve oxygen-carrying capacity. Packed cells are safer and allow processing of the unused plasma for other products. There is authoritative agreement that 80 percent to 100 percent of transfusions for increasing oxygen capacity should be in the form of packed cells.[27,28] The use of packed cells can be improved through increased staff interest and cooperation. The use of packed cells in the community hospital previously mentioned increased from 30 percent of transfusions to 60 percent between 1972 and 1974 as indicated in Table 3. Since 1974 the staff has mandated that all transfusion units for routine use be given as packed cells. The advantages of using packed red blood cells are indicated in Table 4.[26] Indications for red blood cell therapy are listed in Table 5.[29] The various components resulting from the separation depicted in Figure 1 are listed with major complications in Table 6.[31] Indications for various components are listed with the alternatives in Table 7.[31]

When a transfusion reaction is thought to have occurred, the transfusion should be stopped immediately. The reaction must be investigated in an organized manner as indicated in Table 8.[10]

How can we, as individual physicians, improve usage of blood? This can be done by (1) justification of blood use, (2) use of appropriate component, (3) use of a transfusion sheet for the medical record (requiring justification by a physician) and (4) encouragement of and participation in an active transfusion committee.

TABLE 6.—*Blood Components and Complications*

Material	*Content*	*Major Complications*
Whole blood	One unit = 450-500 ml.	Hepatitis, fever, chills, allergic reactions, circulatory overload, rare hemolytic reactions and malaria.
Red blood cells	One unit = 250-300 ml. (yield from one unit of whole blood)	Same as for whole blood but with reduced risk of circulatory overload.
Washed	Same	Same as for RBC but fewer toxic and allergic reactions and probably less risk of hepatitis.
Frozen	Same	Same as for RBC but probably less risk of hepatitis and reduced reactions from leukocytes and platelets.
Platelet-rich plasma	One unit = 200-250 ml. (yield from one unit of whole blood)	Hepatitis, fever, chills, allergic reactions, circulatory overload, development of antiplatelet antibodies.
Platelet concentrate	One unit = 10-30 ml. (yield from one unit of platelet-rich plasma)	Same as for platelet-rich plasma except no circulatory overload.
Granulocyte rich plasma or concentrate	Granulocytes from 10 units of normal whole blood	Hepatitis, fever, chills, allergic reactions.
Plasma, single donor, (fresh, fresh-frozen, or aged)	One unit = 200-250 ml. (yield from one unit of whole blood)	Hepatitis, fever, chills, allergic reactions.
Antihemophilic factor, single donor	100 Factor VIII units in 25 ml.	Hepatitis, fever, chills, allergic reactions, hemolysis due to isoagglutinins.
Antihemophilic factor, multiple donor	250 Factor VIII units in 25 ml.	Same as in AHF.
Hemofil	750 Factor VIII units per 25 ml.	Same as AHF.
Factor IV complex	500 Factor IV units per vial	Hemolysis due to isoagglutinins, very high risk of hepatitis, fibrinolysis (low risk).
Fibrinogen	1 or 2 grams per vial	Hemolysis due to isoagglutinins, hepatitis, fibrinolysis
Albumin	5 grams per dl in 250 and 500 ml 25 grams per dl in 20, 50, 100 ml	Rare
Plasma protein fraction	5 grams per dl in 50, 100, 250 and 500 ml	Rare
Immune serum globulin	16 grams per dl in 2 and 10 ml	Rare
Rh_o (d) immune globulin	1-1.5 ml per vial	Rare

AHF = antihemophilic factor RBC = red blood cells

TABLE 7.—*Indications for Blood Products*

Indications	*First Choice*	*Alternatives*
Severe anemia with hypovolemia (acute hemorrhage)	Whole blood	Red cells plus a plasma expander
Severe anemia without hypovolemia	Red cells	Washed frozen red cells if high risk of allergic reaction
Severe anemia with hypervolemia or diminished cardiac reserve	Red cells; plasma-phoresis if necessary	Same
Severe thrombocytopenia	Platelet concentrate	Platelet-rich plasma
Granulocytopenia with sepsis	Granulocyte-rich plasma	Buffy coat fraction from normal donor blood
Coagulation defects:		
Hemophila (factor VIII deficiency) with severe anemia	Red cells with AHF	Fresh, whole blood with AHF or fresh-frozen plasma
Hemophilia without severe anemia	AHF	Fresh-frozen plasma
Parahemophilia (factor V deficiency) without severe anemia	Fresh-frozen plasma	Fresh plasma
Parahemophilia with severe anemia	Fresh whole blood	Red cells and fresh-frozen plasma
Factor II, VII, IX, or X deficiency without severe anemia	Fresh-frozen plasma	Any preparation of plasma
Congenital factor II, VII, IX, or X deficiency with severe anemia	Red cells, plus either plasma or factor IX complex	Fresh whole blood
Congenital hypofibrinogenemia	Fibrinogen (only when bleeding occurs)	None
Low serum albumin	25 percent salt-poor albumin may be moderately effective	None
Low serum globulin; exposure to hepatitis A	Immune serum globulin	None
Prevention of Rh immunization	Rh_o (D) immune globulin	None

AHF = antihemophilic factor

TABLE 8.—*Investigation of Transfusion Reactions*

Specimens needed
- A. Pretransfusion blood of recipient.
- B. Post-transfusion blood of recipient.
- C. Pilot samples of donor blood
- D. Blood from container implicated in reaction.
- E. Posttransfusion urine.

Investigation procedures (letters refer to specimens listed above)

Immediate
- Examine for visible hemolysis (A,B,E)
- Repeat ABO (A,B,C,D)
- Repeat Rh (A,B,C,D)
- Direct antiglobulin test (A,B)
- Check cross match report and identification of donor and patient

Definitive
- Repeat major and minor cross match (A,B,C)
- Repeat antibody screening (A,B,C)
- Special techniques as necessary
  - Microscopic examination of negatives
  - Prolonged incubation
- Bacteriologic smear and culture (D)

Corroborative
- Identification of any irregular antibody of incompatibility

Optional
- Haptoglobin (A, B)
- Methamalbumin (A, B)
- Bilirubin (B)
- Urea (B)
- Hemosiderin (E)

Dr. Greenwalt,[32] Medical Director of the American Red Cross, has stated that, in the future, "Each donation will serve many patients and whole blood transfusion will be a historical curiosity."

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Appendix

Standards for Blood Banks and Transfusion Services

I. General Policies and Definitions

A. All phases of the selection of blood donors and of the collection, storage, processing, and transfusion of blood shall be the responsibility of a qualified, licensed physician with a thorough knowledge of blood bank methods and of transfusion principles and practices.

B. There shall be an adequate staff to carry out the various phases of a blood transfusion service under his supervision.

C. Suitable quarters and equipment shall be available to maintain safe and acceptable standards.

II. Donors and Donor Blood

A. Criteria for donor selection:
These shall be applied on the day of donation by suitably trained persons and the results shall be appropriately recorded.

1. It shall be determined that the blood donation will not be detrimental to the donor. The following minimum requirements shall apply:

a. Prospective donors with a history of chronic diseases of the heart, kidneys, lungs, liver and so forth, or with a history of cancer, of abnormal bleeding tendencies or of convulsions after infancy shall be excluded subject to evaluation by a qualified physician on the day of donation.

b. Except for reasonable qualifying circumstances, the interval between individual donations should be at least eight weeks.

2. The donor shall be free of disease transmittable by blood transfusion as ascertained at the time of collection in accordance with the guide for donor requirements.

3. A guide for donor requirements

a. General appearance
The donor shall appear to be in good health and free from acute respiratory diseases.

b. Age
Blood donors shall be between the ages of 17 and 65 (up to 66th birthday) with the following exceptions:

(1) Donors between ages of 17 and 21 must have a written consent signed by a parent or guardian, unless local law defines the legal age for blood donation as 18. Since laws defining minors vary from state to state, particularly relating to those who are married or on active duty in the federal armed services, legal opinion should be obtained.

(2) After the 66th birthday, donors may be accepted at the discretion of the blood bank physician if they have specific written consent from a physician within two weeks before the date of donation provided they meet all other criteria for acceptability.

c. Temperature
The oral temperature shall not exceed 37.5° C (99.6° F).

d. Hemoglobin or hematocrit
The preferred method is determination of the hemoglobin concentration.

(1) The hemoglobin level shall be no less than 12.5 grams per dl for female donors, and no less than 13.5 grams per dl for male donors.

(2) The hematocrit value, if substituted, shall be no less than 38 percent for women and no less than 41 percent for men.

e. Pulse
The pulse shall indicate no pathological cardiac irregularity and should be between 50 and 110 beats per minute.

f. Blood pressure
The systolic blood pressure should be between 100 and 200 mm of mercury and the diastolic between 50 and 100 mm of mercury. Prospective donors with diastolic blood pressure readings between 100 and 110 mm of mercury and donors with abnormal differences between their systolic and diastolic pressures may be accepted only after evaluation by a qualified physician.

g. Pregnancy
Existing pregnancy or pregnancy during the preceding six months disqualifies a prospective donor.

h. Dental surgical procedures
Tooth extraction or other minor oral surgical procedures during the preceding 72 hours shall exclude a donor.

i. Receipt of blood or blood components
Donors who during the preceding six months have received blood or those human blood components known to be a possible source of hepatitis shall be excluded.

j. Infectious diseases
A donor shall be free of infectious diseases known to be transmittable by blood insofar as can be determined by usual examination.

(1) Viral hepatitis
Donors with a history of viral hepatitis as well as those who within six months have had close contact with a person having the disease shall be excluded.

(2) Malaria
If the prospective donor has ever had a definite case of malaria, or is an immigrant or visitor from an area considered endemic by the Malaria Program Center for Disease Control, United States Department of Health, Education, and Welfare, he is permanently rejected. Travelers in areas considered endemic for malaria may be accepted as regular blood donors six months after return to the United States provided that they have been free of symptoms and have not taken antimalarial drugs. Those who have taken antimalarial prophylaxis shall be deferred for three years after cessation of suppressive therapy. All military personnel who have been in an endemic area should be considered to have received suppressive therapy whether or not they say they have. Donations to be used for the preparation of plasma, plasma components or fractions devoid of intact red blood cells are exempted from these restrictions.

(3) Immunizations or vaccinations
Symptom-free donors who have been immunized with toxoids, or killed viral, bacterial or rickettsial vaccines are acceptable after 24 hours. Included are tetanus, typhoid, paratyphoid, cholera, diphtheria, typhus, Rocky Mountain spotted fever, influenza, polio (Salk), plague and prophylactic rabies duck embryo vaccines.

Smallpox: Donors are acceptable either after the scab has fallen off or two weeks after an immune reaction.

Measles (rubeola), mumps, yellow fever, oral polio vaccine and animal serum products: Donors are acceptable two weeks after their last injection or ingestion.

Rabies (therapeutic): Donors will be deferred until one year after their last injection.

k. The skin at the venipuncture site shall appear free of lesions.

l. Obvious stigmata of narcotic or alcoholic habituation or intoxication shall exclude a donor.

m. Allergy
A history of an attack of drug allergy within six months or presently symptomatic allergy such as asthma, hay fever or urticaria are causes for deferment. Donors with symptomatic allergy such as hay fever or urticaria may be accepted if the condition is not active at that time and if they have not received a hyposensitization injection within 72 hours.

n. Weight and amount of blood
Donors weighing 110 pounds (50 kg) or more may ordinarily give 450±45 ml of blood, in addition to pilot samples which shall not exceed 30 ml. Donors weighing less than 110 pounds may give proportionately less in a reduced volume of anticoagulant, provided the standards outlined earlier are met.

Refer to: Petty TL, Newman JH: Adult respiratory distress syndrome (Medical Progress). West J Med 128:399-407, May 1978

Adult Respiratory Distress Syndrome

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Adult respiratory distress syndrome is a common respiratory emergency which follows a variety of severe direct and indirect lung insults. Major features are severe respiratory distress, diffuse pulmonary infiltrations, reduced compliance and refractory hypoxemia due to shunt effect. Surfactant abnormalities may play a role in the mechanical derangement of lung function. Supportive care with mechanical ventilation and positive end expiratory pressure results in survival of approximately 50 percent of patients. Only minimal abnormalities in lung function are found in long-term survivors.

THE ADULT RESPIRATORY DISTRESS SYNDROME (ARDS) is best defined as clinical-pathophysiological state characterized by severe dyspnea, hypoxemia and diffuse bilateral pulmonary infiltrations following acute lung injury in previously healthy persons, usually with no prior major lung disease. This review describes the clinical presentation, discusses the current state of our knowledge of pathogenesis and presents an approach to systematic, physiologically oriented management. Prognosis and late sequellae of ARDS are also reviewed.

Historical Perspective

ARDS is not new to medicine. Our original characterization of ARDS[1,2] cited earlier descriptions of the pathologic conditions related to ARDS, previously termed congestive atelectasis.[3] Today ARDS is recognized as an important clinical state and is better understood and better managed, although substantial problems with management remain. Rapidly growing interest in ARDS has resulted in an increasing number of editorial comments, some using other names for the syndrome,[4-6] and some controversy over the appropriateness of the use of ARDS as a proper designation of the clinical syndrome has surfaced.[7,8]

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Two multidisciplinary conferences concerning ARDS served to indicate that ARDS occurred following a variety of unrelated lung injuries[9,10] and that many loosely used clinical terms, listed in Table 1, actually refer to the same entity (ARDS).

ARDS was first described as a clinical syndrome[1] in 1967. In 12 patients clinical features were reported that were believed "remarkably similar to the infantile respiratory distress syndrome." Ventilatory management with positive end expiratory pressure (PEEP) was also first reported in ARDS in that article, although the technique of PEEP had been described earlier.[11] Five patients survived. Autopsy findings in the seven who died showed striking alveolar atelectasis, engorgement of capillaries and hyaline membrane formation.[1]

Shortly after this, in February 1968, a conference on the pulmonary effects of nonthoracic trauma was conducted in Washington, D.C., by the Committee on Trauma of the Division of Medical Sciences, National Academy of Sciences—National Research Council.[9] Discussion of the pulmonary effects of shock accompanying multiple long bone trauma and following resuscitation often involving large volumes of fluid showed that the pulmonary features had a monotonous regularity and a striking similarity to those in our original description of ARDS.[9] Many of the presentors were clinicians who had cared for combat casualties in Vietnam. It was believed that a large number of cases coming to the attention of physicians was due to huge numbers of

TABLE 1.—*Other Terms for Adult Respiratory Distress Syndrome*

Shock lung
Traumatic wet lung
White lung syndrome
Capillary leak syndrome
Acute alveolar failure
Post-perfusion lung
DaNang lung
Congestive atelectasis
Adult hyaline membrane disease

combat casualties cared for by "alert informed physicians whose minds have been sensitized to detect the unusual and the unexplained."[9] The excellent battlefield resuscitation and prompt evacuation to surgical care facilities made it possible for persons who previously would have died to receive medical attention.

The mechanisms of acute lung injury *were and remain unknown,* but speculations regarding toxic factors or vasoactive substances, the pulmonary effects of fat embolization, lung ischemia, surfactant abnormalities, hemodynamic factors and exogenous factors such as overtransfusion of fluids were considered as possibly involved in the pathogenesis of ARDS.

One of us (T.L.P.) reported 21 cases at this conference. A new therapeutic approach was described which included mechanical ventilation with a newly designed volume respirator, PEEP, fluid restriction and corticosteroid drugs. In this series, 11 of 14 patients survived with the use of PEEP compared with only 3 of 8 during our earliest experience where PEEP was not used. There was, therefore, a suggestion of improved survival with PEEP in this early series ($p = < 0.05$).[12]

Later a clearer clinical description of ARDS was offered, stressing clinical features, factors influencing prognosis and principles of management,[2] and the 16th Aspen Lung Conference on acute pulmonary injury and repair dealt with basic science and clinical aspects of ARDS.[10] Subsequently there have been many excellent studies originating from other centers that have added greatly to our understanding of ARDS.

Clinical Setting and Clinical Presentation

The clinical onset of ARDS may be dramatic or insidious. Often there is a latent period between the initial injury (such as shock or multiple trauma) and the subsequent full development of the clinical, roentgenographic and pathophysiological features.

TABLE 2.—*Adult Respiratory Distress Syndrome*

A. *Clinical Signs*
Pronounced dyspnea
Tachypnea
Labored respirations
Intercostal retractions
Cyanosis, refractory to oxygen therapy
B. *X-ray and Physiologic Signs*
Diffuse bilateral pulmonary infiltrates
Reduced lung and chest wall compliance $\Delta V/\Delta P$ (measured on ventilator)
Increased alveolar or inspired to arterial oxygen tension difference
Improved pulmonary oxygen transport with positive end expiratory pressure
High minute ventilation (spontaneous or with a ventilator)

Since ARDS occurs following a variety of direct and indirect lung insults the clinical presentation as well as the manifestations of the clinical syndrome itself will be a consequence of the type of injury. These findings are summarized briefly in Table 2. Respiratory distress, labored respirations, diffuse monotonous bilateral infiltrates and profound hypoxemia are hallmarks of the syndrome. The respiratory rate and minute ventilation are high.[13]

Interestingly, the physical examination is not often very revealing. The labored respirations are obvious, and cyanosis, known to be an unreliable sign of hypoxemia, may or may not be present. On auscultation of the lungs very few abnormal sounds are heard in spite of the pronounced respiratory distress and massive pulmonary infiltrations of the fully developed syndrome. Specifically the bubbling rales of cardiogenic pulmonary edema, the rhonchi of secretions in large airways and the crackling rales of pulmonary fibrosis are not heard. One generally hears a harsh short inspiratory phase and a rather normal expiratory phase during mechanical ventilation. Cardiac sounds are usually normal with no third or fourth heart sound and no valvular murmurs unless there is associated myocardial trauma.

Pathophysiology

Laboratory determinations measured at the bedside with the patient receiving mechanical ventilation help show the pathophysiology in a clinically useful way. Overall pulmonary compliance, the sum of lung and chest wall compliances, is notably decreased. This can be easily measured in patients receiving mechanical ventilation by dividing the delivery pressure of the

ventilator into the tidal volume delivered by the machine. Maintaining static pressure on the lungs and thorax by holding the lungs at end inspiration by occluding the exhalation manifold, or by using the inflation hold control available on some respirators, allows a static compliance measurement to be made. In our original series of 12 patients the overall effective compliance ranged from 9 to 19 ml per cm of water compared with normal values in our laboratory of 75 to 125 ml per cm. This is evidence of the notably impaired overall compliance due to "stiff lungs." High minute ventilation (which is many times more than 20 liters per minute) is present and can be measured with a simple hand spirometer (Wright, for example) or calculated from ventilator rate and tidal volume. Profound hypoxemia is usually present in spite of high inspired oxygen fractions, with accompanying hypocarbia due to the high minute ventilation.

The difference between inspired and arterial oxygen tensions is indicative of the difficulty with oxygen transfer across the lung and is probably a more useful bedside test than the measurement of alveolar to arterial tension difference during ventilation with 100 percent oxygen, as is commonly done in some intensive respiratory care units. We prefer this method of assessing the impairment in oxygen transfer across the lungs because it deals with the arterial tension at which the patient is receiving mechanical ventilation and avoids the artifact of increasing the alveolar arterial tension difference on 100 percent oxygen breathing which converts low ventilation perfusion regions into shunt regions.[2] The underlying physiological basis for the gas transfer abnormality is severe ventilation-perfusion ($\dot{V}_A\dot{Q}$)[14] mismatch and wasted ventilation which affects arterial oxygenation a great deal more than carbon dioxide elimination. A true diffusion defect may be present as well due to interstitial edema, hyaline membrane formation and a reduced capillary blood volume.[15,16]

The basis of the mechanical derangement of ARDS lungs is not clearly known. Increased elastic and surface forces are present and are considered in the discussion of surfactant below.

Roentgenograms of the Chest

The features seen on x-ray studies of the chest are monotonously similar despite the many different pathways to the development of ARDS. Generally diffuse, bilateral dense alveolar infiltrates are present without pleural effusions or enlargement of the cardiac silhouette, unless there is a related myocardial injury or pericardial effusion as a consequence of the original lung injury (Figure 1). It must be stressed that the x-ray features are not specific for the nature or degree of acute pulmonary insult and do not accurately correlate with the degree of physiologic abnormality present. Occasionally infiltrations are somewhat unilateral, often in the presence of direct lung trauma with contusion (Figure 2).

Figure 1.—Typical x-ray appearance of ARDS in 46-year-old woman following severe hemorrhagic shock. Note bilateral alveolar infiltrates with air bronchograms.

Theories of Pathogenesis

It is apparent that the lung can be injured by insults delivered via the airways or circulation.[17] Causes leading to these remarkably similar clinical features include shock from any cause (hemorrhagic, cardiogenic, septic or even anaphylactoid),[18] multiple trauma including massive fat embolization,[19] diffuse intravascular coagulation,[20] endotoxin,[21] paraquat poisoning,[22] drowning,[23] overwhelming viral pneumonias,[24] massive aspiration[25] and central nervous system injury[26] including trauma and drugs (especially narcotic drugs).[27,28] Therefore, many possibilities concern-

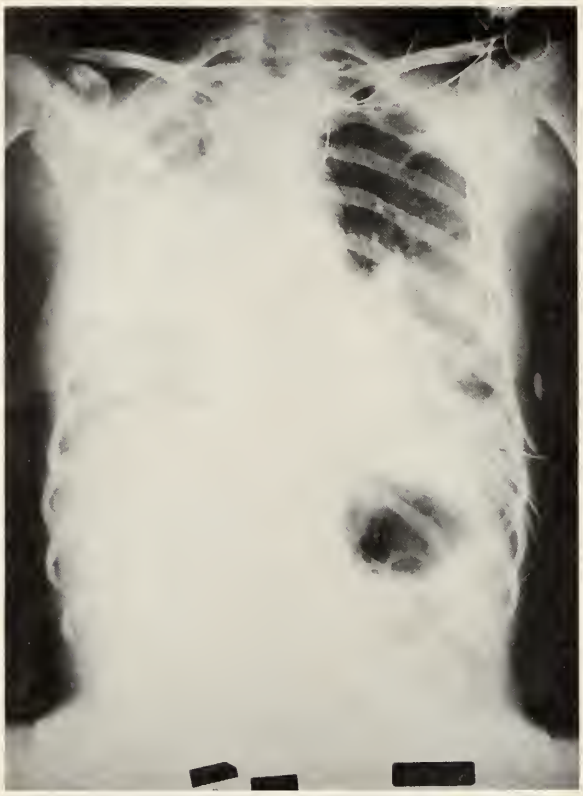

Figure 2.—X-ray appearance of lung contusion in ARDS following automobile trauma in 34-year-old woman. Severe contusion of right lung is present.

ing the exact mechanism of injury exist. Possible agents or mechanisms involved in diffuse lung injury are cited in Table 3.

From the above a "final common pathway" must occur following these diverse insults which injure the lung *either* via the inhaled route or via the circulation. There is strong evidence to support the hypothesis of increased capillary permeability leading to "capillary leak."[25,30,31]

Pathological Findings

The lungs are heavy, airless and appear like liver in cut sections. Alveoli are collapsed, and a hemorrhagic infiltration with debris and hyaline membranes are found lining alveolar spaces. These pathologic features are nonspecific and represent the final common pathway of massive diffuse lung injury.[1,9]

Experimental Models

Several experimental models have been used to produce a clinical-pathological syndrome in some ways similar to ARDS. The most widely used is the injection of oleic acid into large animals, mostly dogs.[32] A chest trauma model producing pulmonary contusion[33] and a hemorrhagic shock model also caused features similar to those in ARDS in dogs[34,35] and in primates.[36]

TABLE 3.—*Possible Causes of Adult Respiratory Distress Syndrome*

Leukocytes
Platelets
Humoral agents
Immunological reactions
Neurogenic shock
Oxygen
Microemboli
Toxins
Overhydration
Viral infections
Complement

Various disturbances of brain function, including anemia and shock, lead to abnormalities in brain oxidative phosphorylation. These are believed operative in ARDS and form the basis for "neurogenic models."[26,36] The likelihood of a neurogenic mechanism is supported by evidence that denervation of one lung offers protection against damage, with severe lung edema occurring in the contralateral innervated lung.[36,37]

High oxygen concentrations have been used to create a pattern of lung injury in lambs similar to that found in ARDS; this same injury did not occur in lambs receiving ventilation in a similar manner with air.[38] This model supports the belief that oxygen-induced injury is a major factor in further lung injury during the treatment of ARDS in humans[39,40] (see discussion of oxygen and ventilation below).

Leukocytic sequestration occurring in experimental hypotension with release of proteolytic enzymes,[41] the effect of platelet aggregates[42] with release of humoral agents and the mechanical effects of cellular microemboli are believed to play a role in lung injury at least in experimental models and possibly in ARDS.[43,44] An aspiration injury model using hydrochloric acid with a pH of 1.8 on a dose weight basis in dogs offers an additional experimental approach.[45]

Although the scientific advantages of an experimental model are obvious, species differences in lung structure and differences in response to various types of injury make comparisons of these models difficult. Their relevance to ARDS, consequently, is subject to question.

Role of Surfactant Abnormalities

The increased elastic recoil of ARDS, the shared features with the respiratory distress syndrome of the newborn[46] and the suggestion of surfactant

abnormalities in some,[34] but not all[35] of the above cited experimental models have focused attention on possible surfactant abnormalities in ARDS. A primary surfactant abnormality cannot, of course, be implicated, but the possibility of surfactant inactivation in states of pulmonary edema has been raised.[47] Secondary surfactant abnormalities could then contribute to the pathogenesis of ARDS.[48] The hypothesis is that alveolar atelectasis would augment the transudation of pulmonary edema and hemorrhage, thereby leading to massive focal atelectasis. The fact that a latent period of often 12 to 24 hours or more occurs between acute lung injury and the development of ARDS is intriguing in this regard since it is known that surfactant half-life (on release from the type II pneumocyte) is approximately 18 to 24 hours after experimental pulmonary embolization and recovery.[49]

Considerable evidence exists that type II cells and probably surfactant production can be damaged by high oxygen concentrations, which are often required for life support in severe states of ARDS.[50,51]

Although our original report suggested surfactant abnormalities from observations made on minced lung specimens,[1] it was not until recently that we were able to show abnormalities in surfactant compressibility and in the isopycnic density of the alveolar lipoprotein aggregates in a fresh specimen from a patient with ARDS following severe hemorrhagic shock.[52] Shortly thereafter we found similar abnormalities in surfactant function in five additional ARDS cases due to septicemia and narcotic overdose with aspiration alone and hemorrhagic shock, respectively.[53]

Therefore, although the role of surfactant abnormalities remains speculative the existence of surfactant abnormalities is now strongly suggested. The role of surfactant in the further pathogenesis of ARDS following the initial injury and its role in the mechanical improvement which can be observed clinically (see below) on recovery parallels the necessary time for recovery and regeneration of type II cells. Both the experimental and clinical observations, therefore, have credibility in relation to the pathogenesis of ARDS.

Incidence

The true incidence of ARDS in the United States today is not known. This is due largely to lack of uniformity and agreement on definition, and no effective reporting mechanism. The task force of the lung division of the National Heart, Lung and Blood Institute has estimated that at least 150,000 cases are identified and treated each year.[44] The true incidence is probably much greater.

Management

Prevention

Ideally ARDS should be anticipated and prevented. This means the avoidance of fluid overload whenever possible, the utilization of the lowest possible oxygen fraction for adequate tissue oxygenation and, at least in the case of multiple long bone fractures, the institution of corticosteroid drugs to prevent or anticipate the adverse effects of free fatty acids on the lung in the dramatic syndrome of fat embolization.[19] There are other considerations for steroids discussed below.

Supportive Management

Many reviews describing the current state of the art have been offered.[2,30,48,54,55] In brief, the treatment of the full-blown syndrome is primarily supportive and requires the placement of a definitive airway and mechanical ventilation using a ventilator with high pressure and flow capability. An endotracheal tube can be placed initially and is suitable for short-term management, such as two to four days. Endotracheal tubes can be left in place longer but they have the disadvantages of poor patient comfort, are an inferior route for suctioning and do not usually allow the patient to take nourishment by mouth.

A volume ventilator providing high pressure and flow capability and accurate control of the inspired oxygen fraction is required. The ventilator provides mechanical work and allows modification of pressure wave forms. The Monaghan 225 and 228 respirators and the Bennett MA-1 respirator, along with others, offer the necessary pressure and flow capabilities required in most cases of ARDS. To avoid possible oxygen toxicity, it is important to reduce the inspired oxygen fraction as rapidly as possible while maintaining adequate oxygen transport across the lungs commensurate with tissue demands. The possibilty of further oxygen induced injury must be minimized with the use of the lowest possible oxygen fraction. Most modern ventilators have accurate control of oxygen fraction delivery. These have been summarized in various textbooks. The time-

dose threshold in producing oxygen toxicity in man remains unknown. An extensive review considers this subject.[56,57]

Positive end expiratory pressure also improves oxygen transport across the lung by reducing shunting.[1,2,13,57,61] Very likely, lung units are recruited with the use of PEEP. Functional residual capacity is clearly increased.[60,61] Since pressures on the order of 5 to 15 cm water are generally all that is required, it is unlikely that cardiac output will be significantly reduced.[62] Some investigators employ much higher levels of PEEP.[63]

In some circumstances tissue oxygen transport may, in fact, be reduced by PEEP[38,64] and the possibility of barotrauma may be increased in high levels of PEEP. Therefore, a concept of optimal PEEP is emerging.[65,66] Optimum PEEP as judged by systemic oxygen transport, usually occurs within the best compliance region ($\Delta V/\Delta P$) of mechanical ventilation.[65,66]

Initially the mechanical ventilator is adjusted with a fairly high tidal volume of 12 to 14 ml per kg and the machine used in the assister-controller mode. The routine measurement of pressure-volume curves of lungs and thorax is recommended in order to establish the tidal volume and PEEP level which exist within the region of best overall compliance.[65,67]

It is preferable whenever possible not to paralyze patients. Even with crush injuries of the chest many patients will allow the ventilator to provide the work of breathing in the combined assister-controller mode with a rate chosen appropriate for the patients' needs. The application of the modern ventilator of course must be guided by frequent arterial blood gas determinations.

Fluid Management

Proper fluid management is essential in maintaining an adequate circulation and avoiding further complications. Whereas aggressive fluid therapy was the rule in shock management before the characterization of ARDS,[68] it subsequently became clear that fluid overload is an important complicating factor in ARDS.[1,2,13,55] Fluid sequestration in the lung is probably facilitated by increased capillary permeability. In addition, fluid retention as a response to ventilator management via excessive antidiuretic hormone activity is a likely complicating factor.[69] Nonetheless adequate systemic perfusion is mandatory in order to maintain organ system integrity including the lung.[70]

The choice of fluid replacement remains controversial. Albumin replacement to restore the delicate Starling relationship between hydrostatic and colloid pressure has been suggested in patients with ARDS and interstitial edema who are hypoproteinemic.[71] Other experimental evidence indicates, in contrast, that lung water may actually be increased with the use of colloid compared with crystalloid infusions.[72] For this reason and on the basis of bedside clinical experience, the authors today prefer the use of crystalloid solutions. Diuretics such as furosemide or ethacrynic acid are also employed if there is overt evidence of fluid overload and systemic circulation is satisfactory. In the most difficult cases one often walks the proverbial tightrope—balancing between fluid administration, monitoring evidence of adequate perfusion such as systemic blood pressure, adequate urine flow (such as 25 to 30 ml per hour), and the avoidance of overhydration using the pulmonary capillary wedge pressure measured through a Swan-Ganz catheter as a guide.[73] Renal function may become a relatively low priority during this period and mild to moderate azotemia is common. Even advancing renal failure should not demand a pronounced increase of fluid infusion.

Adjunctive Pharmacologic Management

Certain groups of drugs are commonly used during the ventilatory support phase of ARDS care. A brief commentary on corticosteroids, antibiotics and fluid management follows.

Corticosteroids have a theoretic benefit by their ability to prevent or reduce aggregation of leukocytes which may cause damage by the release of proteolytic enzymes within the lung. Some authors have offered the view that corticosteroids are protective in the face of endotoxic shock by reducing the activity of lysosomal enzymes.[74,75] Methylprednisolone has increased the survival rate in dogs with lung injury induced by oleic acid.[76] It has also been suggested from observations in humans and in experimental animal models that corticosteroids are effective in fat embolization.[19,77] Also, improved mechanics was found in excised rat lungs following exposure to high oxygen concentrations, with improved survival with corticosteroids compared with controls.[78]

Against the use of steroids is their potential effect of reducing lung bacterial clearance, shown

in experimental studies.[79] We have reported that sepsis complicating ARDS remains an unsolved enigma.[80]

Whether or not steroids have other therapeutic benefits or disadvantages is not known. In practice, the authors use methylprednisolone sodium succinate (30 mg per kg of body weight, given intravenously in divided dosage) for the first 24 to 48 hours. In theory this will capitalize upon the beneficial effects and minimize long-term side effects such as sepsis and oxygen toxicity.

Antibiotics

The use of prophylactic antibiotics is to be condemned. In a review of our earlier experience there was no evidence that the use of prophylactic antibiotics in any way prevented infection with dangerous Gram-negative bacilli.[80] Therefore, use of antibiotics should be reserved for identified infections and then guided by culture and sensitivity tests.

Strategies of Care

The priorities are (1) adequate arterial oxygenation (for example, arterial oxygen saturation [SaO_2], 90 percent) and adequate circulating hemoglobin to maintain oxygen content; (2) adequate cardiac output (for example, sufficient for mixed venous oxygen pressure [Po_2] greater than 30 mm of mercury) and (if possible to observe) adequate mentation or integrated central nervous system responses, warm extremities and some renal flow, (3) lowest possible fraction of inspiratory oxygen (FIO_2), ideally to 0.6 or less within 24 hours and to 0.5 or less after two or three days. Naturally there are trade-offs in these strategies and, of course, the *bottom line* is adequate oxygenation and maintenance of brain function.

Weaning

Mechanical ventilatory support is required until the patient recovers sufficiently to support his or her own ventilation, and to adequately transfer oxygen without PEEP. Briefly, the chest must be stable, the patient alert and cooperative and PEEP no longer required. PEEP should not be reduced until the inspired oxygen concentration can be reduced to 40 percent (FIO_2 less than 0.4) and then PEEP should be reduced in 3 cm of water increments with repeated monitoring of blood gases both initially and one hour after each reduction. At this stage, if oxygen transport is adequate, short trials with a T-piece attached to the endotracheal tube or tracheostomy collar are made with blood gas monitoring at 30 to 60 minute intervals. If blood gases are maintained and the patient remains comfortable, the ventilatory assistance is no longer needed and the endotracheal tube or tracheostomy can be removed, if not needed as an independent airway. Further details of useful weaning techniques in ARDS are cited elsewhere.[81]

Prognosis

The immediate outcome in ARDS involves three basic factors: (1) the degree of original lung injury, (2) the success of initial resuscitation and support of the patient and (3) the avoidance of complications and further injury. Certainly there are patients whose lung injury is so severe that survival is not possible. These patients often die shortly after they reach the hospital. Properly applied support methods will generally permit the immediate survival of most patients in spite of severe lung injury. Modern mechanical ventilators provide sufficient work capability to support the ventilation of even severely damaged lungs. In most patients adequate oxygenation can be accomplished at the onset with high inspired oxygen fractions (tensions); however, this is at the cost of potential further lung injury from oxygen toxicity. It must be emphasized that it is extremely important to minimize the likelihood of oxygen toxicity by carrying out mechanical ventilation with the lowest possible inspired oxygen fraction (see principles of management). Avoidance of septic complications is equally important.

Observations can be made at the bedside which are good prognostic indicators. Patients with the best compliance and the best and most prompt blood gas response to PEEP are most likely to recover.[82] Open lung biopsy studies in those with more unfavorable physiologic measures showed the greatest cellular and fibrotic changes.[82]

The comparison of survival rates from various institutions is difficult because of different selection criteria. Our own experience in 100 consecutive patients managed at our center, beginning with our first case, from 1966 to 1975, is cited in Table 4. It is evident that the overall survival is not improving, but it must be stressed that eight patients in whom liver transplantation was done, all of whom died with sepsis, are included in the

last 50 cases. Without these special cases the survival rate in our overall series is 49 percent which is similar to that in other series.[44]

Sequellae on Recovery

Late sequellae are surprisingly infrequent. In a series of ten patients with ARDS requiring mechanical ventilation for from 3 to 36 days (mean 13.5 days) from an FIO_2 greater than 0.6 for 2 to 13 days (mean 4.6 days), four were entirely asymptomatic and six had only mild to moderate symptoms when carefully evaluated 4 to 42 months after recovery (mean 23 months).[81] The physiological abnormalities were only mild to moderate and included both obstructive and restrictive ventilatory abnormalities, a moderate diffusion defect which tended to improve with time, and normal blood gas values at rest, but slight hypoxemia during exercise. Others have reported similar findings.[82,83] A reevaluation in nine of our original patients (follow-up 39 to 83 months after ARDS) showed a further improvement in patients with a restrictive ventilatory defect and stable minimal airflow obstruction or normal lung function except in one person with underlying chronic obstructive pulmonary disease.[84] Interestingly, airway hyperreactivity with increased response to methacholine was found in two of 7 patients tested.

The morphologic basis for lung recovery from severe diffuse injury is suggested by the work of Bachofen and Weibel[16] who have shown that the type I alveolar lining cell is geometrically too complex to replicate and, therefore, if injured, dies. Type II or so-called metabolically active cells, however, can proliferate and differentiate into type I cells to reestablish the alveolar capillary membrane.[16] That this occurs is highly suggested by the gradual improvement shown in forced vital capacity, functional residual capacity, single breath diffusion tests and arterial blood gas studies on recovery.[83-86]

The Future

We need to understand mechanisms of disease and how the lung responds to injury and how repair may occur without fibrosis. We desperately need markers of injury by which we can detect ARDS *before* the advanced syndrome is recognized clinically. We must find ways to induce oxygen tolerance and protect the lung from sepsis. We must learn the role of surfactant abnormalities in the pathogenesis of the syndrome. So far, new approaches to support using an extracorporeal oxygenator for partial oxygenation of severely injured patients have not proved more successful than conventional means of support. A few long-term survivors have been reported, however.[87,88] It is possible that this form of support would be more successful if applied to less severe cases. The key to success is to protect the lung from further injury during the life-support period and the challenge is to reduce the risk of sepsis and oxygen toxicity.

TABLE 4.—*Survival in Adult Respiratory Distress Syndrome*

Year	*1967*[1]	*1972*[80]	*1975*
Patients	12	51	100
Survived	5	21	45
Percent	42	41	45

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Specialty Conference

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Refer to: Mellon M, Incaudo GI, Kahler S, et al: An approach to the treatment of asthma—University of California, San Diego, School of Medicine, and the University of California Medical Center, San Diego (Specialty Conference). West J Med 128:408-418, May 1978

An Approach to the Treatment of Asthma

WILLIAM L. NYHAN, MD, PH D:* *The subject of this conference is asthma. We shall illustrate the problem by presenting the case of a patient who had had a long-standing and difficult problem.*

STEPHEN KAHLER, MD:† The patient was a 15-year-old white girl who had had onset of wheezing at the age of three. She had had approximately two episodes of wheezing each year and had never been admitted to hospital or given any medication until, at the age of 8 years, when the family moved to Santee, California, she began to wheeze every day. Treatment was started with tablets containing ephedrine sulfate, theophylline and hydroxyzine hydrochloride (Marax®), and she received 25 to 30 tablets a week. She was missing about 30 days of school a year.

She was seen first at University Hospital when she was ten years old. It was clear that her asthma was at least partly allergic in nature. She had other allergic signs and symptoms, including itchy eyes and palate, runny nose and allergic shiners. Her environmental situation in Santee was felt to be quite heavily contributory to her problems. She slept on a wool covered couch in the living room, where there was a shag carpet. She used a feather pillow. The family kept four dogs and four cats, and countless stuffed animals in their home. An attempt was begun at environmental control, and immunotherapy was started. The Marax tablets were continued. In the following year, decongestants were added. She continued in relatively poor control until the end of 1973, when she missed three months of appointments, and came in to the clinic wheezing quite badly. She was treated with oxytriphylline (Choledyl®) and prednisone. Her condition did not improve. She was admitted to hospital and rapidly deteriorated while receiving aminophylline by injection and hydrocortisone (Solu-Cortef®); an isoproterenol (Isuprel®) infusion was required.

Following this admission, treatment was begun with cromolyn sodium by inhalation. Steroids were taken orally every other day. She was readmitted about seven months later and then again a few months later at the end of 1974, when administration of salbutamol was begun. In the spring of 1975 she was admitted twice, about two weeks apart, and after the second admission she was discharged receiving aminophylline and salbutamol orally and beclomethasone dipropionate (Vanceril®) by inhalation. She occasionally used metaproterenol by inhalation. Since then, she has had two more admissions to the hospital while oral administration of prednisone was being tapered. The most recent admission was in March 1977.

With the current regimen of Vanceril, salbutamol and theophylline (anhydrous) and glyceryl guaiacolate (guainfenesin) (Quibron®), she has been doing extremely well. She has no longer been receiving orally given steroids; immuno-

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therapy has been discontinued, and she has been essentially asymptomatic. She won a trophy in Little League baseball during the summer. Her environment problems, which had a lot to do with her wheezing were only gradually resolved. The dogs stayed in the house for a long time and contributed to her problem. There were also family quarrels and numerous psychosocial problems in the family, some of which have since been resolved.

ROBERT N. HAMBURGER, MD:* This discussion is not simply about this little girl who was one of our patients in recent years with a happier outcome. Her case does point out that the outpatient management of this type of intractable, almost crippling asthma, has changed considerably from what was described above and has become complex enough to be discouraging to general clinicians. We would like to outline an approach, primarily for outpatients with severe, chronic or intractable asthma.

With today's patient we utilized many approaches. First, one of our Allergy Physician's Assistant Instructors made home visits and spoke to the family a great number of times, trying to get the patient and family cooperation that we need in this type of illness. In this patient there was a major amount of allergic disease as well as hyperreactivity of the lung that we do not fully understand. The environmental approach was an important aspect of her care. More recently, through self-hypnosis, we have taught her how to relax when she begins to feel the onset of bronchospasm. We and the social worker tried to help the family through some very difficult social situations. Therefore, even though today we are going to emphasize primarily a drug approach to the treatment of asthma, we do not lose sight of the fact that the treatment must be approached from every angle necessary in a given patient: environmental, social and psychological therapy as well as immunotherapy are employed in addition to drug therapy. A scoring method for the grading of the severity of an asthma attack is shown in Table 1. This may be helpful in deciding upon admission to hospital versus outpatient treatment.

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TABLE 2.—*The Association of Atopic Disease With IgE*

IgE-IU/ml		*Percent Adult Population*	*Incidence of Allergic Diseases*
Birth to 2 Years	*3 years to Adult*		
<10	<100	68	5
10-20	100-350	20	20
21-100	351-750	9	35
>100	>750	<3	±100*

*In the absence of helminthiasis.

The question is frequently asked, "How useful is measurement of the serum level of IgE in the diagnosis of allergic disease?" Whether it is allergic asthma, rhinitis, or eczema, the extent to which IgE measurement may be helpful is illustrated in Table 2. This shows four basic intervals for two groups. The first group is of infants through two years of age; the second, children from three years up to and including adults. The lower intervals are below 10 IU per ml in infants and below 100 IU per ml in others. We find 68 percent of the adult population at this level. We are not certain yet what percent of infants are in this population—and it will require more data to find out—but it may be about the same proportion because both have a very low incidence of allergic disease.[1] In the interval 10 to 20 IU per ml in infancy and 100 to 350 IU per ml in older children, a fifth of the population is found. The data were obtained in a predominantly Caucasian population in the United States. Data from Japan and other places in Asia, as well as from

TABLE 1.—*Clinical Score for Severity of Asthma**

	0	*1*	*2*
Pa_{O_2} mm of mercury	70-100 in air	<70 in air	<70 in 40% O_2
Cyanosis	None	in air	in 40% O_2
Inspiratory breath sounds	Normal	Unequal	Decreased to absent
Accessory muscles	None	Moderate	Maximal
Expiratory wheezing	None	Moderate	Pronounced
Cerebral function	Normal	Depressed or agitated	Coma

A score of 5 or more indicates impending respiratory failure—obtain blood gas determinations, notify anethesiologist.

A score of 6 may require transfer to the intensive care unit.

A score of 7 or more with a Pa_{CO_2} of 65 mm of mercury indicates existing respiratory failure.

*Adapted with permission from Wood DW, Downs JJ and Lecks HI: Amer J Dis Child 123:227-228, 1972.

certain areas of Africa, suggest that median IgE levels may be somewhat higher. There is a significant incidence of allergic disease above 100 IU per ml in adults, and at this level fully 20 percent of the population will be allergic. In the next interval, from 21 to 100 IU per ml in infants or 351 to 750 IU per ml in older children, 9 percent of the population is found but fully a third of them are troubled with significant allergic disease. In the highest interval, that is, over 100 IU per ml in infants or over 750 IU per ml in the older group, if we can rule out parasite infestation with Ascaris or hookworm, virtually 100 percent have significant allergic disease. These data are in international units; to convert them to the approximate figure in nanograms one must multiply by 2.4. As a routine screening procedure, measurement of the serum level of IgE is not warranted. In selected cases, when trying to distinguish atopic from nonatopic disease or, as in the case discussed today, how much of the disease is IgE mediated and how much is caused by other problems, this measurement may be of some help. In the present case, the serum level of IgE was over 500 IU per ml when the patient was 11 years old.

A sequential approach, then, must include environmental control, oral administration of antihistamines when indicated, and the use of specific allergen desensitization when indicated. These three approaches are of most value when we are dealing with an asthmatic patient with strong allergies. In most asthmatic patients, even among infants and children, the disease is not simply IgE mediated but might be called "mixed asthma"; that is, there are many other factors contributing to the disease.

In our approach to the treatment of children with asthma today, we rarely use Marax®, Tedral® or Quadrinal® in chronic asthma. We determine drug therapy for each patient. We begin with a single drug and add medications sequentially. Therefore, we begin with theophylline, and this is followed by some of the new beta agents, particularly the ones that can be taken by mouth, and then cromolyn by inhalation and the new inhaled steroid beclomethasone dipropionate, which is called Vanceril® in this country and Becotide in England, Canada and Mexico. We shall begin with a consideration of theophylline by Dr. Incaudo.

Gary I. Incaudo, MD:* Despite the fact that theophylline was first popular and its use initiated more than 40 years ago for the treatment of asthma, it remains our first approach to drug therapy and provides a base upon which to build a therapeutic program for asthmatic patients. The reasons for this are probably two-fold. First, medical science has yet to develop an agent that is as uniquely effective, well tolerated and safe to administer over prolonged periods as theophylline in the treatment of asthma. In addition, recent advances in theophylline pharmacokinetics and the availability to clinicians of theophylline blood level determinations have made it possible to maintain maximum therapeutic benefits from this medication without troublesome side effects.

The pharmacologic activity of theophylline is thought to reside in its ability to increase cyclic 3′,5′-adenosine-monophosphate ($_c$AMP), by inhibiting the enzyme, phosphodiesterase, the major metabolic enzyme responsible for converting active cyclic AMP to the inactive 5-AMP form. It is this accumulation of cyclic AMP in the cell that mediates smooth muscle relaxation and inhibits the release of histamine from mast cells.

As is the case with many drugs in clinical medicine, the effectiveness of theophylline can be closely correlated with blood levels which are assumed to mirror what can be attained at the receptor sites. For theophylline, concentrations between 5 and 20 μg per ml have been shown to correlate with clinical relief of bronchospasm with transient or minimal adverse reactions.[2] Within this range of 5 to 20 μg per ml, one occasionally sees mild central nervous system stimulation, self-limited diuresis and insomnia.

Theophylline levels in excess of 20 μg per ml become increasingly associated with unacceptable, or even potentially lethal, side effects despite a significant therapeutic benefit from the drug. At levels of 20 to 30 μg per ml, approximately 25 percent of patients experience some gastrointestinal symptoms, such as epigastric pain, nausea, vomiting and occasionally diarrhea.[3] Headaches of peculiar intensity and severity are also reported at this level. At levels in excess of 40 μg per ml, arrhythmias, expressed by the patient as palpitations, are encountered. Occasionally, seizures may occur at this level, but are more commonly manifested at levels in excess of 60 μg per ml. In general, at theophylline serum

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levels above 25 μg per ml, approximately 75 percent of patients will experience some toxic manifestation.

Maintaining a mean serum theophylline level of 10 μg per ml will generally provide significant therapeutic benefit without troublesome side effects. This is our goal in therapy, and it requires monitoring of blood levels as a guide.

Theophylline clearance rates vary widely from person to person, and interestingly even within the same person at different times.[4] Among a group of otherwise normal asthmatic children the half-life of theophylline in the serum has been reported to vary from two to ten hours. The time may be extended to as long as 24 hours in the presence of heart failure or chronic liver disease. Additional recently published data have shown that in an otherwise normal asthmatic child the clearance rate may vary plus or minus 20 or 30 percent over one to eight months. A decrease in the elimination rate to such a degree would result in drug accumulation with continued administration at the same level and result in potential toxicity. This has not been a frequent problem in our experience but one should be alert to the possibility. We can conclude that for maximum effectiveness and safety it is necessary to monitor blood levels of theophylline, both chronically as an outpatient and acutely as an inpatient in the treatment of asthma.

Current guidelines for the oral administration of theophylline in a continuous manner provide for a standard dosage regimen and the use of timed blood samples at appropriate intervals.[5] For children who have had no theophylline-containing preparations in the previous 24 hours, we recommend a loading dose of 7.5 mg per kg of body weight of anhydrous theophylline, which is designed to yield a serum level between 10 and 20 μg per ml. Subsequent doses are started at 5 mg per kg of body weight every six hours. This dose may be increased 1 mg per kg of body weight every six hours as indicated at no less than three day intervals until the desired therapeutic effect is obtained, toxicity intervenes or until a dose of 7 mg per kg of body weight is reached. At this dosage, Weinberger has reported that 25 percent of children will have peak serum concentrations in excess of 20 μg per ml and hence be at risk for toxicity.[6] Any further increase is dictated by the clinical need and monitored with blood levels, usually obtained about two and six hours after an oral dosage (Table 3).

TABLE 3.—*Guidelines for the Administration of Theophylline*

Oral Theophylline Administration

1. Loading dose: 7.5 mg/kg of anhydrous theophylline
2. Maintenance therapy: Range of 4-10 mg/kg/6 hours of anhydrous theophylline with a median dose of 7.0 mg/kg/6 hours at which 25 percent of children have concentrations in excess of 20 μg/ml.

Intravenous Theophylline Administration

1. Loading dose: 5.6-6.0 mg/kg will, on the average, raise the serum theophylline by 10 μg/ml.
2. Maintenance therapy: Continuous
   Mitenko: 0.9 mg/kg/hr. of aminophylline
   Loughnan: 1.25 mg/kg/hr. of aminophylline
3. Maintenance therapy: Intermittent
   20-30 mg/kg/24 hours of aminophylline in divided doses up to every 6 hours.

In the treatment of status asthmaticus with intravenous administration of aminophylline, the most recent data (Table 3) indicate that among healthy adults an intravenously given loading dose of 5.6 mg per kg of body weight, followed by 0.9 mg per kg per hour produces levels between 5 and 15 μg per ml in 95 percent of patients.[7] In asthmatic children the same loading dose followed by 1.25 mg per kg per hour as a continuous infusion results in a similar range. This is consistent with earlier finding that theophylline is eliminated in children at a more rapid rate than in adults. These data were not obtained in a therapeutic trial with clinically ill asthmatic patients. Therefore we currently recommend that a loading dose of 5 mg per kg be used if the patient has not received theophylline in the previous 24 hours, followed either by continuous infusion of 1 mg per kg per hour, or by intermittent administration at 4 mg per kg given by slow infusion every four hours. If further increase is indicated clinically, blood levels should be obtained before any increase. In most asthmatic patients, therapeutic levels will rapidly be achieved by this approach.

DR. NYHAN: *The role of the beta adrenergic agents will be discussed by Dr. Michael Mellon.*

MICHAEL MELLON, MD:* If a patient with asthma is receiving appropriate doses of theophylline and has attained what should be therapeutic serum levels of theophylline, but is still symptomatic, then a $beta_2$ adrenergic agent should be added. The $beta_2$ agents are very useful in the treatment of asthma because of a rapid onset of relief of

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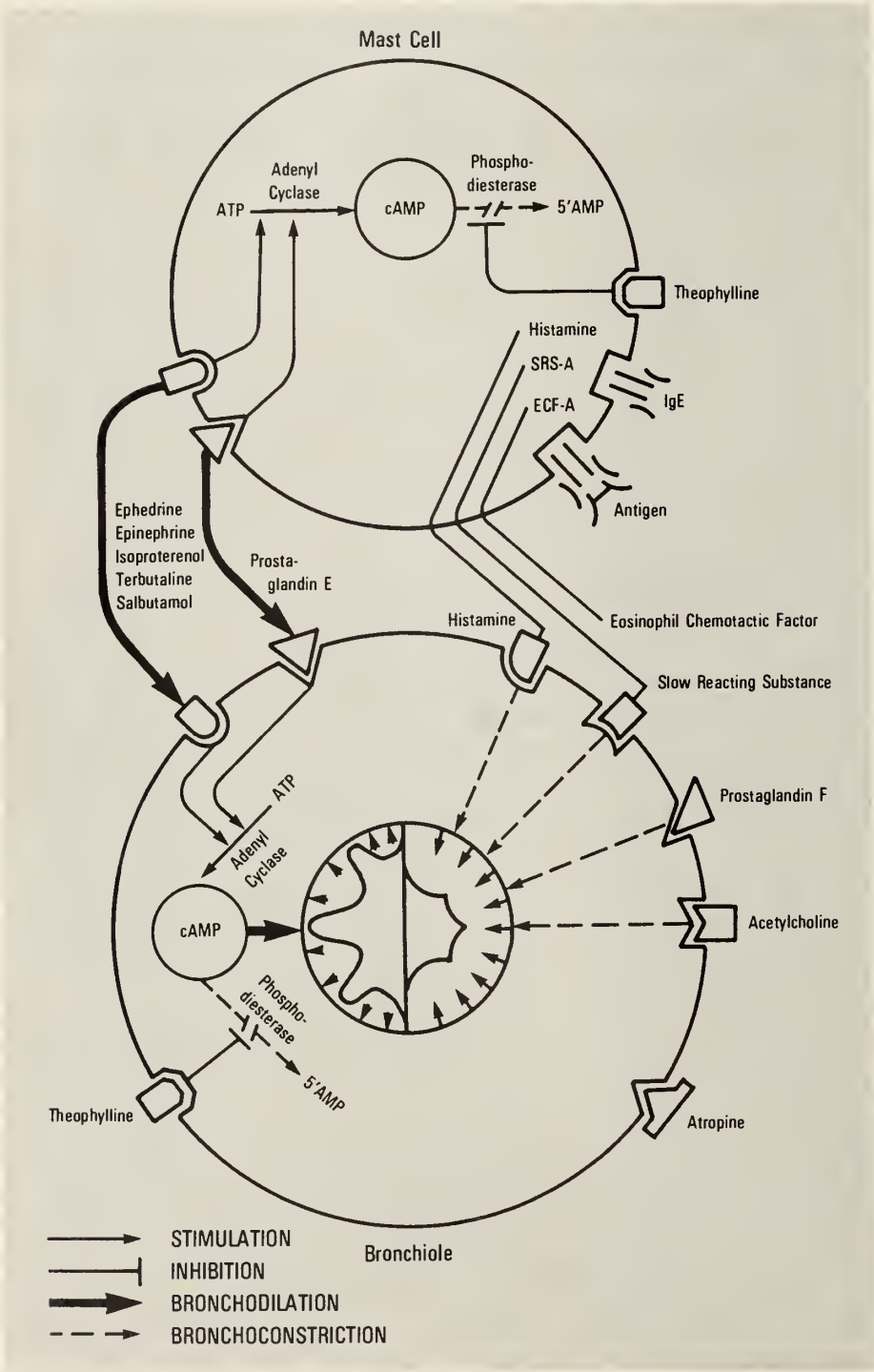
bronchoconstriction and because of their ease of administration. However, they have short durations of action and have many side effects. There is also a tendency for patients to abuse these agents, especially in the aerosol form. This limits their usefulness for treating outpatients. Currently, there are 14 different $beta_2$ agents available throughout the world, and the search is continuing for selective $beta_2$ stimulation with no $beta_1$ side effects and also for a sufficiently long duration of action to permit usefulness for outpatients.

The basic physiology of the action of these agents is reviewed in Figure 1. Represented

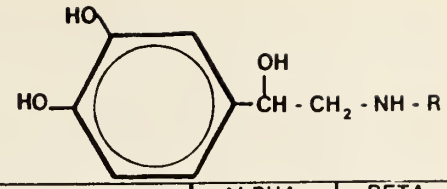


5'AMP = 5'adenosine monophosphate
ATP = adenosine triphosphate
cAMP = cyclic adenosine monophosphate
ECF-A = esosinophil chemotactic factor of anaphylaxis
SRS-A = slow reacting substance of anaphylaxis

Figure 1. — Schematic representation of the mast cell and bronchiole showing membrane associated events leading to changes in intracellular cyclic AMP levels with inhibition or enhancement of mediator release or subsequent bronchoconstriction or bronchodilatation.

schematically, the mast cell is at the top and the bronchiole on the bottom. The $beta_2$ receptors are located in the membrane of the mast cell and in the wall of the bronchiole. When the $beta_2$ receptors are stimulated, they in turn stimulate the activity of adenyl cyclase, which results in an accumulation of cyclic AMP intracellularly in the mast cell or the basophil and also in the bronchial wall. The action of theophylline is to inhibit the phosphodiesterase catalyzed breakdown of cyclic AMP. Accumulation of cyclic AMP intracellularly in turn inhibits the release of histamine, slow reacting substance of anaphylaxis (SRS-A) or eosinophilic chemotactic factor of anaphylaxis (ECF-A). In the cells of the bronchioles increased cyclic AMP itself is thought to cause bronchodilation directly. In summary, therefore, the $beta_2$ adrenergic agents work in two places: inhibiting mediator release and directly on the bronchiole.

In 1960 Lands reported the physiological differences, between the $beta_1$ and $beta_2$ receptor, permitting for the first time an understanding of how some agents could be so efficacious and yet cause so many side effects.[8] The $beta_1$ receptors are located in the heart and in adipose tissue. They mediate increases in contractility and cardiac rate and also lipolysis. The $beta_2$ receptors have many functions but the one that we are most interested in is dilation of the bronchiolar smooth muscle. It is interesting to note that isoproterenol hydrochloride (Isuprel®) is the most potent stimulator of both $beta_1$ and $beta_2$ receptors and the order of potency between norepinephrine and epinephrine changes when one goes from $beta_1$ to $beta_2$. The important two things



R	ALPHA EFFECTS	BETA EFFECTS
H - NORADRENALINE	++	±
CH - ADRENALINE	++	++
CH(CH3)2 - ISOPRENALINE	±	++
C(CH3)3 —	o	++

Figure 2.—Effect of varying N-alkyl substituent on relative α- and β-effects in sympathomimetic drugs.

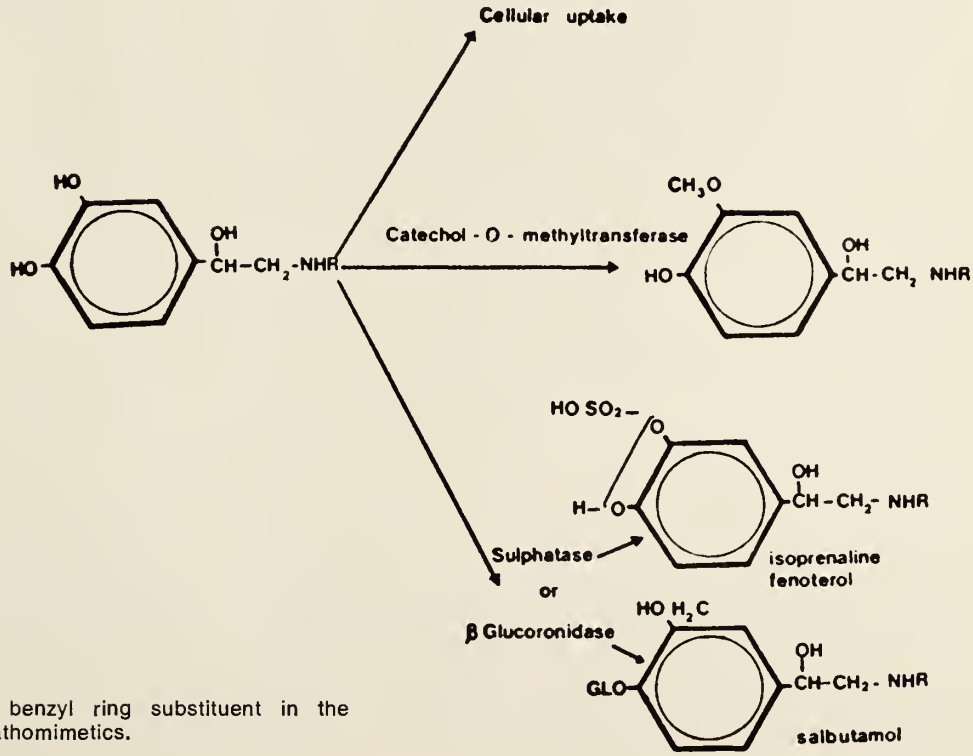


Figure 3.—Effect of benzyl ring substituent in the inactivation of sympathomimetics.

in synthesizing a new $beta_2$ agent are to produce an agent that has almost pure $beta_2$ selectivity and has a long duration of action.

Figure 2 shows the basic catecholamine structure. Our discussion will focus on the R-group that is believed to control $beta_2$ specificity. The smaller the R-group the less $beta_2$ specificity and the more generalized alpha and $beta_1$ stimulation. In the case of norepinephrine where R is only a hydrogen ion, one gets almost pure alpha stimulation with very little beta activity. As the R-group increases in size, through epinephrine, isoproterenol and finally to terbutaline, the $beta_2$ selectivity increases. This is primarily seen with the aerosol preparations because there are changes induced by metabolism in the liver that alter the structure of a compound to produce $beta_1$ activity in some agents in which it would not be expected. The duration of action of these medications is governed by the main metabolic pathway for the catecholamines, which is through catechol-0-methyltransferase (Figure 3). This enzyme substitutes a methyl group at the ortho position and determines the serum half-life of the agent. Therefore in the synthesis of new $beta_2$ agents, efforts are made to put a large group at the H position in order to increase steric hindrance for the enzyme and thereby obtain drugs that will have a therapeutic action of up to 12 hours.

In Figure 4 are pictured the $beta_2$ agents that are presently available throughout most of the world. Many of them are not yet available in the United States. From analysis of the structure of isoprenaline one would not expect much $beta_2$ selectivity and the duration of action would be expected to be rather short. It is a potent bronchodilator, but its use is complicated by cardiac toxicity, arrhythmias or tremors. It also has a somewhat unique side effect, in that it is one of the few aerosol forms that is able to cause bronchoconstriction and decrease Po_2 by itself. If it is overused, there is a tendency for the patient to become refractory to further use of sympathomimetic agents.

Isoetharine (Bronkosol®) would also not be expected to have much $beta_2$ selectivity. The main modification in isoetharine is an ethyl group in place of the hydroxyl, which does cause it to have more $beta_2$ selectivity than isoproterenol hydrochloride, but it also has a short duration of action and numerous side effects. Isoetharine is mainly administered by nebulizer in children admitted to hospital in status asthmaticus. Intermittent positive pressure has little place in the management of children with status asthmaticus since it does not increase the delivery of the agent to the lungs and may increase the incidence of pneumothorax and pneumomediastinum.

Metaproterenol is marketed in this country as Metaprel® or Alupent®. It is available in an orally given liquid form, 10 mg per teaspoon, or in 20-mg tablets. It is also available in an aerosol form. It has an isopropyl group which increases the $beta_2$ selectivity and the hydroxyl group has been moved to the meta position, giving this agent a duration of action of approximately four to six hours. We have been somewhat disappointed with metaproterenol in the orally administered form. In most cases it has not actually provided much theophylline reduction nor potentiation and has not kept us from having to move on to cromolyn or oral steroids. However, if a patient requires an inhaler in this country today the first choice would be a metaproterenol inhaler. We have been very impressed with the efficacy of metaproterenol given by inhalation, and we have prescribed it for young patients with reliable parents, especially patients who have an episodic type of asthma, and we think that we have prevented emergency room visits with the judicious use of this inhaler. We also have used it with success in those patients who have exercise-induced bronchospasm. The $beta_2$ agents are actually superior to cromolyn and atropine-like drugs in the prevention or relief of exercise-induced bronchospasm.[9]

Terbutaline is a recently synthesized $beta_2$ agent. It has not been approved for use in children under 12 years of age. It has a large substitution at -R- and has more $beta_2$ selectivity than metaproterenol. It also has a hydroxyl group in the meta position giving it a long duration of action. It is available in this country in tablets of 2.5 or 5 mg. Our experience has been that it often causes tremulousness in children under 12 years of age. This can be dealt with by titrating the dose down to 2.5 or 1.25 mg three times per day. Allergists have reported success with it in the treatment of asthma in adults.[10] It is also available in an injectable form to be given subcutaneously as one would give epinephrine. We can discern no significant difference between injectable terbutaline and epinephrine in our clinical experience.

The next agent that I would like to discuss is salbutamol: trade names are Ventolyn®, Albu-

terol® and Proventil®. Albuterol is not available commercially in this country at this time. We have tested this drug as an investigational new drug, and we were very impressed with it. In the orally given form it was clearly superior to any of the other available oral $beta_2$ agents. It has a large substitution with the addition of a methanol substitution and its duration of action is six to ten hours. The form of Albuterol that is probably the most efficacious is the inhaled form. The inhaler is available in Europe, Mexico and Canada, but not yet in the United States. On the basis of reported literature, it has almost no cardiac toxicity, but there is some increased irritability and increased tremulousness seen primarily with overuse of the inhaler.[11] The other two structural formulas, fenoterol and hexoprenaline, in Figure 4 provide a glimpse into some of the changes that will be taking place in asthma therapy in future years when these newest $beta_2$ agents become available. These agents have much greater $beta_2$ selectivity than any of the other agents. They also have much longer durations of action and almost no cardiac toxicity. These two agents do not lose their $beta_2$ selectivity in parenteral use, something that cannot be said for the other agents. These agents have been administered intravenously to patients admitted in status asthmaticus decreasing the need for intermittent positive pressure breathing machines or nebulizers to deliver $beta_2$ agents.[12] Isoproteronol infusion is not used when these agents are available. We can foresee, there-

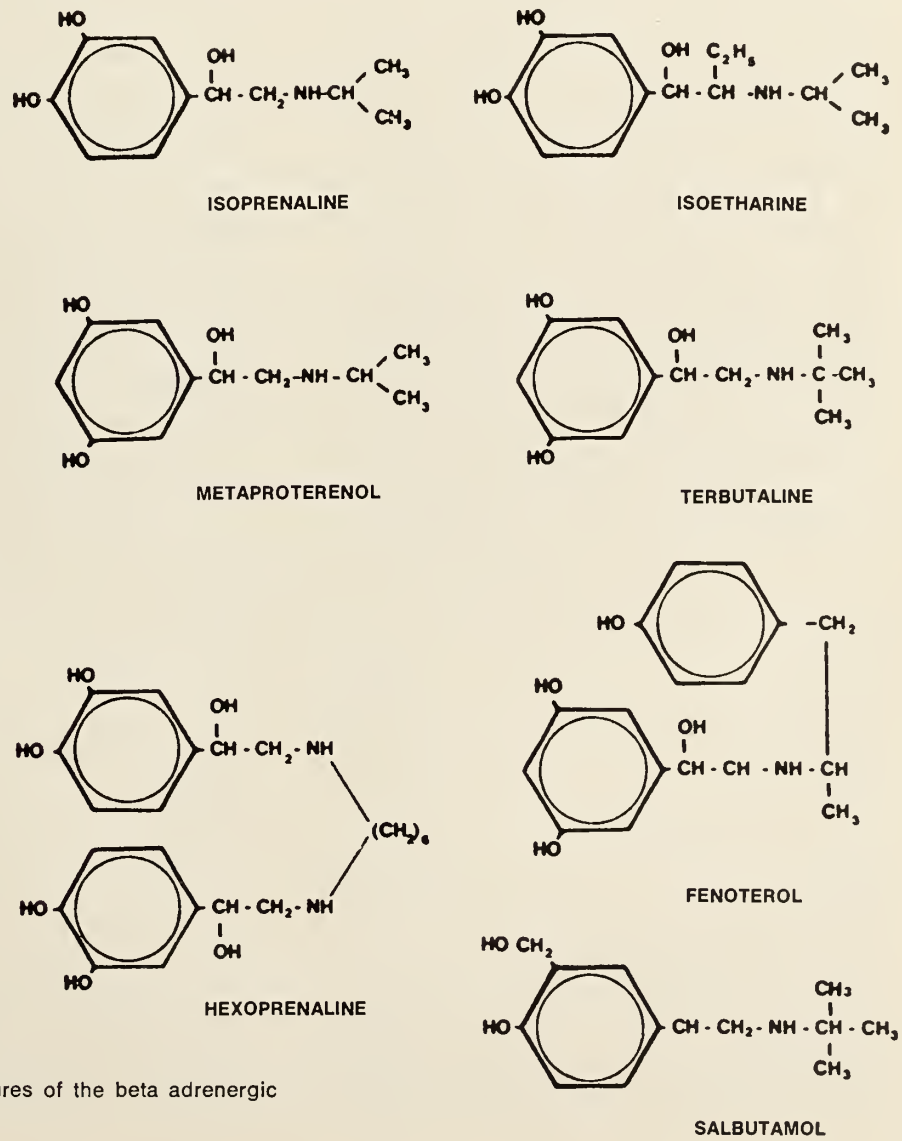


Figure 4.—Molecular structures of the beta adrenergic drugs.

fore, that the newer agents are going to change our therapy of asthma dramatically when they are released for general use in this country.

We do not recommend fixed combination drug preparations when treating asthma. In many studies it has been shown that ephedrine does little or nothing to improve the forced expiratory volume (FEV_1) over the theophylline effect. The only finding attributable to ephedrine was an increased number of side effects.[13] In addition, the amount of ephedrine in fixed combination preparations limits the amount of theophylline that can be safely prescribed.

In summary, the $beta_2$ agents currently available in this country have been rather disappointing. In children under 12 years of age, metaproterenol is the best available; in children over 12 years of age and in adults terbutaline or metaproterenol are the two best agents presently available, and the metaproterenol inhaler can be very useful. The inhaler should be prescribed with the caution that the patient call if he needs to use it more than three or four times in any 24-hour period. With respect to the $beta_2$ agents, it is safe to say that "the best is yet to come."

Dr. Hamburger: We could end our discussion at this point if it were the case that one could control bronchospasm in asthmatic patients with two drugs: theophylline and a $beta_2$ active agent. However, bronchospasm, in combination with edema, inspissated mucus and inflammation may cause many patients to go on wheezing despite full therapeutic doses of both theophylline and a $beta_2$ agent. In such patients, we try cromolyn given by inhalation before steroids. Cromolyn has only been available here since 1973, but it has been used in large numbers of persons in Europe for seven or eight years. Cromolyn was developed by Altounyan based upon the observation that khellin, a plant product, had a bronchodilator effect.[14] He made and studied numerous analogues over a 15-year period before he synthesized disodium cromoglycate or cromolyn, which oddly enough does not have any bronchodilator effect. In fact, there is still a lot of debate as to how it does work, but it is effective in about a third of chronic severe asthmatic patients.[15] Expectation of success in only one of three asthmatic patients might discourage one from trying it, but since we are now discussing the most difficult asthmatic patients to control, it is certainly worth trying. It was thought that a good response would only be seen in the IgE-mediated or allergic asthma. In our experience we more often get a good response to cromolyn in allergic asthmatic patients, but occasionally an "intrinsic" asthmatic will have a good response and certainly it is worth trying in a patient with exercise-induced asthma. Cromolyn is not a bronchodilator; it is a prophylactic medication; it should be given before wheezing becomes evident. It is contraindicated for a person who is actually wheezing, because it will irritate his airway and may in fact produce bronchospasm. There is no point in using inhaled medication such as cromolyn or the inhaled steroid, Vanceril®, unless the small airways have been opened. An inhaled medication must get down to its site of action, the bronchioles, to do some good and this will not occur in active asthma. There is no major toxicity from cromolyn, although it was recently reported that five or six patients in a large series were noted to experience either anaphylaxis or urticaria.[16] These are very rare occurrences. Most side effects consist of mild irritation or cough induced by the inhalation of cromolyn. A trial of cromolyn is probably worthwhile in any chronically asthmatic patient. It takes a trial of at least a month, in a reliable patient who uses the drug systematically, three or four times per day, every day without fail, to know whether cromolyn is useful.

I want to conclude with the last of the new drugs available in this country; called Vanceril®, it is an inhaled steroid, beclomethasone dipropionate. It is called Becotide in Europe, Mexico and Canada. Two puffs, inhaled four times per day, delivers a total of 400 μg of active drug. In other words, a dose of 50 μg is delivered automatically when the cannister is depressed. The patients should be taught to inhale it deeply into the lungs, hold it as long as possible and exhale it through the nose, thereby coating the affected mucous membranes. This material works by direct contact, is very insoluble and is not absorbed to a significant extent; it is, therefore, a significant advance over orally or parenterally given steroids. No adrenal suppression has been observed with the doses recommended, from 200 to 800 μg in 24 hours. Studies have shown that until you exceed 1,600 μg per day, by inhalation, there is no appreciable effect on the adrenal-pituitary axis.[17] Therefore, there is a reasonably

safe differential between the therapeutic dose of 400 μg per day and the beginning toxicity dose of 1,600 μg per day. Furthermore it has been shown that there is usually no advantage to increasing the dose above 800 μg in 24 hours. If improvement is not obtained on that dosage, improvement may not be inducible at any safe dosage in that patient. Consequently, there is no reason to increase above the recommended dose. I would emphasize this very strongly to patients since there is a tendency for patients to use excessive amounts of inhaled medications. A word should also be said about the importance of adequate instruction on the use of each of the inhalers (spinhaler and gas propelled) to the patient. The instructions inserted with the devices are inadequate for most people, and a demonstration, including supervision of the patient's use of the device, is essential.

The advantage of beclomethasone by inhalation is its direct effect in the lung, and the absence of adrenal suppression, growth retardation in children and other signs of steroid effects. Side effects reported to date have been the appearance of monilia in cultures of the mouth and pharynx of a large percentage of the population using inhaled steroid. Clinical monilial infection occurs in only 2 to 3 percent of culture-positive patients. We expect positive cultures very frequently in patients receiving this preparation, and remarkably, so far, those few who have had monilial infections have not been a serious problem and the infections have cleared with simple local care and mycostatin therapy. The question of long-term side effects is worrisome. In the first five years of usage no serious problems have been encountered, but that does not mean that they will not occur. I have been in clinical science long enough to know that most great advances usually produce new problems. But so far the serious problems that have been induced with Vanceril are iatrogenic. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after the transfer from systemic corticosteroids to the aerosol beclomethasone. These occur because the patient who has been treated with orally given steroids for a long period may take months to recover adrenal function sufficient for protection in times of stress. The patient should be warned that in time of stress such as an accident, surgical operation or status asthmaticus, he will need to be protected with exogenous steroid. That a normal adrenal response to stress is present should be proven by the determination of the AM cortisol and adrenocorticotropic hormone response or by the elapse of a year since the last use of parenteral steroids. Another side effect encountered when we wean a patient from orally given steroid to inhaled steroid is the reappearance of other long suppressed allergic problems such as eczema, rhinitis and symptoms in the eye, nose, throat or gastrointestinal tract. These symptoms often require specific therapy such as antihistamines or topical steroids.

At present the only indication for use of a beclomethasone inhaler is for patients who require chronic treatment with orally given or injected corticosteroids to control their bronchial asthma. A Vanceril inhaler is *not* indicated for the relief of asthma which can be controlled by bronchodilators or cromolyn. It is not indicated in patients who require systemic steroids infrequently and it is not indicated in the treatment of wheezing due to nonasthmatic or infectious bronchitis. The Vanceril inhaler is contraindicated in the primary treatment of asthma.

Remember that both cromolyn and beclomethasone are prophylactic and will not be useful—in fact, may make the patient worse—if used during the acute attack of asthma. Either or both of these drugs can produce a pronounced decrease in clinical symptoms of asthma and significant improvement in pulmonary function studies, but weeks of continuous use by inhalation may be required to perceive the total extent of improvement which may be achieved with cromolyn or beclomethasone.

TRADE AND GENERIC NAMES OF DRUGS

Albuterol®	*salbutamol*
Alupent®	*metaproterenol*
Becotide®	*beclomethasone dipropionate*
Bronkosol®	*isoetharine*
Choledyl®	*oxtriphylline*
Isuprel®	*isoproterenol*
Marax®	*ephedrine sulfate, theophylline, hydroxyzine hydrochloride*
Metaprel®	*metaproterenol*
Proventil®	*salbutamol*
Quadrinal®	*ephedrine hydrochloride, phenobarbital, theophylline calcium salicylate, potassium iodide*
Quibron®	*theophylline (anhydrous) and glyceryl guaiacolate (guainfenesin)*
Solu-Cortef®	*hydrocortisone*
Tedral®	*theophylline and ephedrine*
Vanceril®	*beclomethasone dipropionate*
Ventolyn®	*salbutamol*

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Neonatal Silver Nitrate Prophylaxis

ASK THE WOMEN who work in the newborn nursery why they put silver nitrate in a baby's eyes. I bet you will find at least three fourths of them don't know why they do it. And if they don't know what that stuff is for, it is rather easy for them to forget. In the hassle of the delivery room with the mother in pain, or some bleeding going on or maybe somebody going into shock, they sometimes just forget to put it in. But, fortunately, this is a rare happening.

—ROBERT P. BURNS, MD, *Portland, Oregon*

Extracted from *Audio-Digest Ophthalmology*, Vol. 15, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

Refer to: Crohn disease—Newer aspects of etiology, diagnosis and therapy—Medical Staff Conference, University of California, San Francisco. West J Med 128:419-427, May 1978

Crohn Disease

Newer Aspects of Etiology, Diagnosis and Therapy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. MORRELLI:* *This morning's Medical Grand Rounds will be led by Dr. John P. Cello from the Gastrointestinal Unit at San Francisco General Hospital Medical Center.*

DR. CELLO:† In a report published in 1932 in the *Journal of the American Medical Association,* Crohn, Ginzberg and Oppenheimer[1] described and classified a new pathologic and clinical entity that they called "regional ileitis."[1] They described a granulomatous process in the terminal ileum that mainly occurs in young adults and is characterized by a subacute or chronic cicatrizing inflammation. This disease entity, now called "Crohn disease," was actually first described in 1806 by Coombe and Saunders at the Royal College of Physicians in London.[1]

Tremendous strides have been made in our understanding of the clinical aspects of Crohn disease of the bowel over the past few years. We would like to put into perspective the exciting newer developments in Crohn disease, particularly studies on causes and pathogenesis, newer methods of laboratory diagnosis, improvements in diagnostic radiography and advances in the medical therapy.

Etiology

Studies of the pathogenesis of Crohn disease have taken two main paths: *first,* a search for infectious agents, either serologic markers of the agents in the host or isolation *in vitro,* or transmission of the agents to experimental animals; *second,* an attempt to define possible host susceptibility factors that make a portion of the population at risk of Crohn disease developing.

Neither of these avenues of research has produced totally convincing evidence of Crohn disease as an infectious or inherited disease, but the research in this area is provocative.

Search for Infectious Agents

Aerobic, anaerobic, and mycobacterial cultures of bowel specimens from patients with Crohn disease have failed to show any unique organism. The study by Farmer and associates illustrates

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropin
CDAI = Crohn disease activity index
DNCB = dinitrochorobenzene
HLA = human leukocyte A (histocompatibility antigen)
6-MP = 6-mercaptopurine
RNA = ribonucleic acid
SKSD = streptokinase and streptodornase

the search for a viral cause of the disease.[2] In a comparison of 15 patients with Crohn disease with 65 age-matched and sex-matched control subjects, there was no difference in results of serologic tests for a number of viruses between the two groups. In addition, tissue cultures for cytopathogenic viruses failed to show any consistent changes. Some other viral investigations showed differences in the Crohn population, but they have not been confirmed. Recently, electron microscopic, physical and biochemical studies were carried out by Gitnik and Rosen[3] on viral isolates from tissue from patients with Crohn disease in Vermont, England and California; tissue from surgical patients served as the control. The same cytopathic changes occurred in patients from these three areas but not in control groups. Electron microscopic studies showed 90 nm viral-like particles in tissues from patients with the disease from all three areas, but not in the control cultures. These and a few other reports suggest a viral cause for the disease.

Some of the most provocative studies purporting to show a transmissible agent in Crohn disease have come from *in vivo* inoculation studies in which fresh homogenates of Crohn disease tissue have been injected intravenously or intraperitoneally, or into the ileum or footpad of experimental animals.[4-7] The tissues homogenized for the transmission studies had characteristics of classic Crohn disease: thickened bowel wall, deep longitudinal ulcerations and thickened serosal fat (creeping fat). Most researchers used 0.2 μ to 100 μ filtrates of homogenates of a full thickness of fresh bowel wall obtained from patients with active Crohn disease at operation and injected the material into many sites in various animals. In one study,[4] a single inoculum of 0.2 μ to 100 μ filtrates introduced into the ileum of rabbits produced macroscopic changes within nine months similar to those in human Crohn disease. These changes did not occur in rabbits injected with homogenates of normal bowel.

Further evidence for the transmissibility of Crohn disease was obtained from *serial passage* studies in which ileal tissue of rabbits, inoculated many months earlier with a filtrate of homogenates from human Crohn disease tissue, and showing macroscopic and microscopic changes suggestive of Crohn disease, was homogenized and injected into the ileum of other rabbits.[4] Again after a nine-month latency period, nearly 50 percent of these rabbits had changes similar to those of Crohn disease, whereas no changes were observed in any of the control rabbits. Transmission of the macroscopic changes does not occur when the homogenates are subjected to irradiation with cobalt 60, freezing to less than $-20°C$, or autoclaving. These studies suggest that the causative agent is a viable organism that is smaller than 0.2 μ or is capable of deformation so that it can pass through the 0.2 μ filter—that is, either a virus or an L-form of bacterium. Numerous investigators have shown the induction of macroscopic noncaseating, granulomatous changes in other species, such as mice and guinea pigs, after intraperitoneal, intravenous and intradermal injection of filtrates of Crohn disease tissue. Furthermore, the changes were subsequently induced in other animals after two serial animal passages, again suggesting that a transmissible agent is involved in the cause of Crohn disease.

Studies using 0.2 μ filtrates of Crohn disease tissue cultured in hypertonic media have shown growth of a cell wall-defective (L-form) pseudomonas in a large number of patients with Crohn disease.[8] No L-forms were isolated from tissue taken from patients with ulcerative colitis or control subjects. Although these results strongly suggest that a transmissible agent is involved in the cause of Crohn disease, several problems arise: the number of patients and control subjects was small in many of the studies and, more important, the results cannot be replicated in other laboratories. Therefore, despite the data indicating that a unique transmissible viral-like agent might exist, evidence of a transmissible agent in Crohn disease is not clear-cut at present but appears likely.

Host Factors

Numerous investigations of host factors have been carried out in patients with Crohn disease and their blood relatives. The best studies show no difference in HLA-A or HLA-B antigens (histocompatibility antigens) in patients with Crohn

disease.[9] However, it has been well documented that a high frequency of certain HLA antigens occurs in some patients with extensive disease and certain associated conditions. For example, patients with ankylosing spondylitis or sacroiliitis have a higher incidence of HLA B-27 antigen than other patients with Crohn disease. In addition, patients with HLA B-27 antigen may have a higher incidence of pancolonic involvement with either Crohn disease or ulcerative colitis.

Earlier studies suggested that immunologic competence is altered to a pronounced degree *in vivo* in patients with active Crohn disease, but this is now controversial.[10] In the initial studies, the incidence of sensitivity to purified protein derivative was considerably decreased in patients with Crohn disease, suggesting altered delayed hypersensitivity. Other studies suggested that skin reactivity to dinitrochorobenzene (DNCB) and to mumps, Candida, and streptokinase and streptodornase (SKSD) antigens was altered. However, the most recent studies showed that in patients *not taking steroids* skin sensitization to DNCB, mumps, Candida and SKSD antigens is normal. This indicates a normal delayed hypersensitivity immune mechanism. Furthermore, absolute serum levels of immunoglobulins were normal except for the diffuse increase in immunoglobulins during the acute flare state. *In vitro* immunologic studies of patients with Crohn disease have also yielded conflicting results.[11] In an excellent recent review[12] of lymphocytes and cutaneous anergy in 33 patients with Crohn disease who were not taking steroids, the mean total lymphocyte count was within normal limits, but the mean absolute peripheral T-lymphocyte count was reduced and the mean absolute peripheral B-lymphocyte count was elevated. Of the patients, 86 percent were anergic in their ability to become sensitized to DNCB compared with 9 percent of the normal control subjects. This indicates lymphocyte hyporesponsiveness in patients with Crohn disease.

In vitro studies of the isolated peripheral lymphocytes in patients with Crohn disease have yielded interesting results. Stobo and his group studied the *in vitro* cytotoxicity of lymphocytes in patients with inflammatory bowel disease.[13] They were able to show that isolated mononuclear cells of peripheral blood can lyse *in vitro* allogeneic colonic epithelial cells. The cells responsible for the colonic cell lysis are probably killer "K" or null cells with a surface receptor for F_c and not T or B cells. This study found the occurrence of an antibody-dependent cell-mediated cytotoxicity, that can be shown *in vitro,* in patients with inflammatory bowel disease.

Korsmeyer reported for the first time the presence of lymphocytotoxic and double-stranded ribonucleic acid (RNA) antibodies in patients with inflammatory bowel disease.[14,15] A higher percentage of patients with Crohn disease and their families (their first degree relatives who are household contacts and their spouses) had a higher incidence of lymphocytotoxic antibody than normal control subjects.[14] Antibody to double-stranded RNA was also found in a higher percentage of patients and families with Crohn disease than in control subjects.[15] Conflicting results have been obtained in studies of mononuclear cell infiltration in patients with Crohn disease. Pathologically, Crohn disease is characterized by a pronounced increase in mononuclear cell infiltration through the full thickness of the involved bowel wall.[16,17] Studies of isolated human intestinal mucosal cells from patients with Crohn disease showed a notable increase in the number of B cells, which were predominantly IgG-producing cells, compared with cells from normal persons and patients with other types of inflammatory bowel disease. However, in one study apparently no K or null lymphocytes were found in the intestinal mucosa[17] and gamma globulin production by the isolated mucosal lymphoid cells was notably increased. These results are at variance with earlier results, which suggested that the predominant lymphocyte infiltrating Crohn tissue is a T cell and in fact the plasma cells are predominantly IgM-producing cells.[16] Because of the conflicting results obtained to date, no definite conclusions can be made.

Diagnosis

The diagnosis of Crohn disease is based at present largely on findings from clinical history, physical examination, roentgenograms, and pathologic studies of tissue biopsy specimens. A number of years ago several interesting reports indicated an apparent association between levels of serum lysozyme or muramidase and the presence of clinically active Crohn disease.[18-20] However, a good clinical correlation between the lysozyme level and the disease activity and extent of involvement in patients with Crohn disease has not been borne out[19,20] and, therefore, the serum lysozyme level is not now considered a reliable index for clinical use.

Dr. Ruedi F. Thoeni will now summarize the recent developments in the roentgenographic diagnosis of Crohn disease.

Radiology

DR. THOENI:* When Crohn, in 1932, described the clinical manifestations and pathologic changes associated with idiopathic inflammatory bowel disease, he referred to findings in the terminal ileum. Since then, many articles have appeared in the literature reporting additional manifestations of the disease in the jejunum, duodenum, stomach, colon and, more recently, the esophagus. Determining whether or not a barium enema study is indicated for a patient with inflammatory bowel disease and, if so, preparing for the examination present a problem for many clinicians. Even though toxic megacolon is much less common in patients with Crohn disease than in patients with ulcerative colitis and even though a barium enema has never been proved conclusively to promote development of a toxic megacolon, there still exists the danger of perforating a very friable mucosa.[21-23]

Radiographic examination is indicated in cases in which a diagnosis must be established, the extent of the disease in patients with acute exacerbations must be determined or complications must be identified. In patients with fulminant diarrhea, examinations should be done with the greatest care. At all times, a preliminary roentgenogram of the abdomen must be obtained to rule out toxic megacolon. A barium enema study should not be done in a patient whose transverse colon measures more than 7 cm in diameter. If the patient suffers from fulminant diarrhea with blood loss and other systemic findings but does not show evidence of toxic megacolon, a radiographic study should be carried out only if absolutely necessary.

To prepare a patient, a 24- to 48-hour liquid diet before the study is sufficient. Only mild laxatives, such as bisacodyl in an orally given dose of 10 mg, should be administered in the afternoon before the examination. Some investigators do not administer any cathartic,[23] but if a double-contrast barium enema study is planned, use of laxatives is essential. We administer a water enema half an hour before the radiographic examination by carefully instilling approximately 1,500 to 2,000 ml of water as recommended by Goldberg[23] and Laufer.[24] We introduce the barium slowly through a rubber tip, rather than a hard plastic tip, distending the colon only by gravity and not by volume and thereby avoiding rapid distention. Glucagon, 1 mg given intravenously, may be used if there are areas of suspected strictures.

Figure 1.—Double-contrast barium enema study shows aphthoid ulcers **(white arrows)** suggestive of Crohn disease.

In recent years the double-contrast barium enema has been used with increasing frequency to diagnose inflammatory bowel disease, but its usefulness remains controversial.[22,25-27] Use of colonoscopy with a biopsy study allows accurate prediction of the extent of disease. Subtle histologic changes cannot be seen on roentgenograms, but the clinical significance of such microscopic findings has not been established. Double-blind prospective studies comparing findings obtained by double contrast barium enema with those of colonoscopy and biopsy studies are required. Geboes and Vantrappen[28] concluded that colonoscopy is superior to radiography in detection of mucosal changes in patients with Crohn disease; the radiographic results were obtained by secondary double-contrast barium enema examinations. Laufer and co-workers[29] found discrepancies between results of colonoscopy and double-contrast barium enema in only four of 80 patients with clinical evidence of ulcerative colitis or Crohn disease. Examination by double-contrast barium enema involves no more risk to a patient than examination by conventional barium enema.[26]

*Ruedi F. Thoeni, MD, Assistant Professor of Radiology.

Radiologic evidence of "aphthoid" ulcers on a background of normal mucosa (Figure 1), patchy rectal disease, "skip" lesions (Figure 2) and an abnormal terminal ileum (Figure 3) appear to be reliable signs of granulomatous colitis.[24,30] However, these findings are accurate only if the colon is cleaned well and highly dense barium is used. Increased accuracy in diagnosis of colitis leads to appropriate and prompt treatment. In patients with granulomatous colitis, the rectum is often not involved and, consequently, sophisticated, expensive and extensive procedures might be carried out until the correct diagnosis is made. Examination by double-contrast barium enema can prevent this.

It is often impossible to assess the full extent of disease in patients with Crohn disease. Loops of small bowel overlie one another and prevent adequate radiologic visualization. Double-contrast examination of the small bowel via duodenal instillation of air and barium may increase the accuracy of examination of proximal loops of small bowel.[31] Peroral pneumocolon examination of the ileocecal region by oral administration of barium and rectal insufflation of air may increase the accuracy of assessment of this region significantly.[32] Both methods fully distend areas of interest, show mucosal detail and assist in determining whether true stenosis is present or the narrowing is related to spasm representing the so-called "string sign." The correct evaluation of phase and extent of disease permits a clinician to decide on the appropriate therapeutic approach.

An increasing number of reports indicating involvement of the upper gastrointestinal tract in patients with Crohn disease have appeared in recent years.[33-40] A careful search of the literature finds 220 cases of Crohn disease in the upper gastrointestinal tract excluding the small bowel.[33] Of these cases, 57.7 percent involved the duodenum alone, 26.5 percent the duodenum and stomach, and 15.8 percent the stomach alone. In patients with regional enteritis, the overall occurrence of the disease in the esophagus, stomach or duodenum is reported to be between 0.5 percent and 4 percent, and is probably even

Figure 2.—Double-contrast barium enema study in a patient with Crohn disease. Skip lesions in the distal transverse and descending colon are well outlined.

Figure 3.—The cobblestone pattern of the terminal ileum, a classic finding in Crohn disease, is clearly apparent.

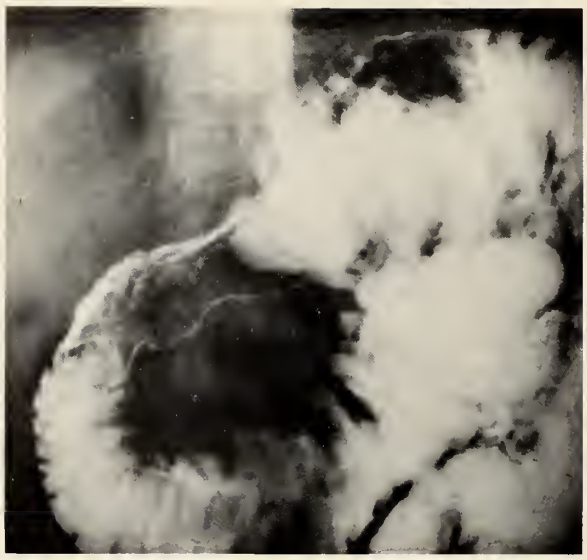

Figure 4.—Double-contrast examination of the upper gastrointestinal tract in this patient with Crohn disease of stomach and duodenum shows the pseudo-Billroth I appearance.

higher.[41] However, Marshak[42] did not find Crohn disease of the esophagus in any of his 8,000 cases of regional enteritis and his 4,000 cases of granulomatous colitis. However, we discovered 24 such cases in the literature of which in at least two there were clearly noncaseating granulomas in the resected specimen.[43,44]

Many reports emphasize showing the presence of typical radiographic features in patients with duodenal, gastric and esophageal Crohn disease. In general, the roentgenographic appearance of Crohn disease in these areas is similar to that of regional enteritis in the ileum. The pseudo-Billroth I appearance involving both antrum and duodenum is especially noteworthy (Figure 4).[41] Reflux into biliary and pancreatic ducts may occur.[45,46] When present on radiograms of these areas in patients in whom regional enteritis or granulomatous colitis is known, radiologists should consider the possibility of Crohn disease involving the stomach and proximal bowel.

The differential diagnosis in Crohn disease can be extensive,[38,41,42,47-49] but a correct diagnosis can usually be made by combining all available clinical, roentgenographic and pathologic findings. Double-contrast barium enema, double-contrast examination of the small bowel and peroral pneumocolon examination of the ileocecal region appear to offer advantages that permit early recognition of extent of disease enabling prompt treatment.

Therapy

Dr. Cello: Medical therapy of Crohn disease consists largely of administration of steroids and antibiotics (both nonabsorbable and broad spectrum antibiotics), and alterations in diet, particularly parenteral hyperalimentation when necessary for patients with active disease. Immunosuppressive therapy has been tried in large numbers of patients with Crohn disease but the results are inconclusive.

Steroids and Adrenocorticotropin

Recent studies have suggested that adrenocorticotropin (ACTH) and hydrocortisone are equally efficacious in effecting beneficial clinical responses in patients with Crohn disease. Previous anecdotal reports suggested some superiority of ACTH over steroids, but studies of treatment with 40 units of intravenously given ACTH and 300 mg of intravenously given hydrocortisone resulted in comparable response rates, plasma cortisol levels and onset of clinical improvement.[50] However, the response to ACTH was less in patients who had been receiving steroid therapy previously. Numerous investigators and clinicians believe empirically that steroid therapy is efficacious in treating the acute flare-up of Crohn disease. Despite the indications that the effects of ACTH and steroids are comparable, steroids such as prednisolone and prednisone are preferable to ACTH for the following reasons: ACTH must be administered parenterally to be efficacious; the response to ACTH in terms of plasma cortisol levels depends on the adrenal status; patients who have received steroid therapy previously respond less well to ACTH; the response to ACTH is less, and ACTH cannot be administered as alternate-day therapy. These reasons clearly suggest the superiority of steroids over ACTH.

Sulfasalazine

Sulfasalazine (the newly accepted name for salicylazosulfapyridine) has been used in the treatment of Crohn disease for many years. Approximately 80 percent of the administered drug reaches the colon unchanged. Presumably because of the action of the colonic flora, the drug is converted to 5-amino salicylate, which may have an anti-inflammatory effect, and sulfapyridine, which might have an antibiotic effect.[51] The therapeutic effects of sulfasalazine are controversial. Unlike the findings of the national co-

operative Crohn disease study (see subsequent section), a recent British multicenter trial using sulfasalazine, 3 grams per day, in 41 patients at nine hospitals over five years did not show a decrease in the relapse rate either after surgical operation or with quiescent disease.[52]

Immunosuppressive Therapy

Until recently immunosuppressive therapy for Crohn disease was considered ineffective. Azathioprine has little or no effect on the natural history of the disease.[53,54] It does not induce or sustain a remission and has a high incidence of toxic reactions. Those earlier results are supported by the recent results of the national cooperative Crohn disease study.

Recently, Present and co-workers[55] reported positive results with the immunosuppressive drug 6-mercaptopurine (6-MP) in 83 patients with intractable Crohn disease. The patients were randomly assigned to either a placebo or 6-MP group after having been declared intractable to medical therapy. At the end of one year the "medications" were switched. The results showed significant clinical improvement with 6-MP compared with placebo. In some patients receiving 6-MP it took as long as four to six months to effect a clinical response. However, 6-MP has a high incidence of toxicity manifested by bone marrow suppression, fever and pancreatitis.

A Comparative Study of Steroids, Sulfasalazine and Azathioprine

The recent national cooperative Crohn disease study[56] of various forms of medical therapy was conducted at 14 medical centers in the United States. In 584 patients with Crohn disease a randomized, prospective double-blind controlled trial was carried out. The activity of the disease and the dose of medication used in the study were determined by a weighted aggregate of clinical measurements that are commonly employed in assessing patients with inflammatory bowel disease—the Crohn disease activity index (CDAI). There were two parts to this study: medical treatment of active symptomatic patients was studied in part I and medical prophylaxis in inactive asymptomatic patients was evaluated in part II. The first part consisted of two phases. During part I, phase I, 300 patients who had active symptomatic Crohn disease were assigned for 17 weeks to either a drug or a placebo. Medications were administered as shown in Table 1.

TABLE 1.—*Administration of Medications in Part I, Phase I of Double-blind Study*

Prednisone
CDAI<150 (mild active disease):
0.25 mg per kg of body weight per day or about 20 mg per day for a 70-kg man
CDAI>300 (severe active disease):
0.75 mg per kg of body weight per day or about 60 mg per day
CDAI=150 to 300: 0.50 mg per kg of body weight per day
Sulfasalazine
1 gram per 15 kg of body weight per day or about 5 grams per day for most patients
Azathioprine
2.5 mg per kg of body weight per day or about 150 to 200 mg per day

CDAI = Crohn disease activity index

In part I, phase II, the 95 patients in whom remission was successfully achieved in phase I were followed for an additional one to two years while receiving a lower maintenance dose of the same drug or placebo that had successfully induced the remission. If a flare-up occurred, the dose was raised to phase I level for one month. In part II, 284 patients with inactive asymptomatic Crohn disease were randomly assigned to the aforementioned drugs or placebo to determine the prophylactic value of these agents in preventing flare-ups of the disease.

Results of part I, phase I, showed that prednisone or sulfasalazine, but not azathioprine, caused a significantly better clinical response than placebo in the control of active Crohn disease. Furthermore, only prednisone therapy resulted in significant improvement in the radiographic appearance of the bowel. In patients with Crohn disease of the colon, sulfasalazine was clearly superior to prednisone, azathioprine and placebo in controlling active Crohn disease. In part I, phase II, none of the drugs was superior to placebo in maintaining a remission once it was achieved. In part II no difference was noted between the drug and placebo groups in prevention of relapses. Toxicity with azathioprine was frequent.

Broad Spectrum Antibiotics

At the University of California, San Francisco, broad spectrum antibiotics have been used in patients who did not respond to conventional medical therapy. Although no double-blind controlled study has been carried out, Moss, Carbone and Kressel[57] have reported impressive results in 44

patients treated with ampicillin, tetracycline and clindamycin or erythromycin (or both). Of the 44 patients, there was dramatic clinical improvement in 41, and resolution of radiographic changes occurred in 20 of 35 patients who received various combinations of broad spectrum antibiotics.

Parenteral Hyperalimentation

Parenteral hyperalimentation is commonly used in treating patients with active inflammatory bowel disease,[58-60] but effects have not been evaluated by good, controlled studies. Hyperalimentation causes a decrease in stool frequency. This rests the bowel and may allow closure of enterocutaneous fistulas. In patients who receive hyperalimentation before surgical operation for inflammatory bowel disease, there is improved nutrition with positive nitrogen balance, weight gain and improved fluid and electrolyte balance before and after operation. However, no study has documented a decrease in the necessity of operation in patients with Crohn disease treated with hyperalimentation. Pneumothorax, septicemia, and episodes of hyperglycemia and hypoglycemia are common effects of this method of treatment. Cholestasis with an increase in serum alkaline phosphatase and even acute acalculus cholecystitis have also been reported with hyperalimentation.

Summary

Extensive progress has been made in our understanding of Crohn disease. The most important recent information to date is probably the clinically relevant data obtained in the National Cooperative Crohn's Disease Study. The efficacy of sulfasalazine and prednisone in the treatment of acute disease is now established.

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Clues in Cultures of Blood Specimens

THERE ARE CLUES that one can use as to what type of blood specimen culture to take in a patient. The age of a patient may give you a clue as to what organisms to suspect. Certainly a newborn infant has a different kind of flora that causes infection and disease than does a child or an older patient. In newborns there are two organisms that are responsible for almost all of the serious infections—the enteric Gram-negatives, with Escherichia coli being the most common, and then the streptococci—so that you could predict pretty well what kind of organism you might find in a newborn suspected of having sepsis. It becomes a little more difficult as the child grows older. Children are likely to be infected with a wider variety of organisms and certainly adults are affected with an even wider variety. But one also has additional clues. Is the patient in the hospital or is he coming in from the outside? The patient who is in the hospital is exposed to organisms which you know are going to be common organisms associated with infection in the intensive care unit—the pseudomonades, the enterobacteria—those organisms which because of the hospital environment have the opportunity to get into the patient. And then, of course, the history of the patient is important: Are you dealing with a patient who has a chronic underlying disease and therefore is susceptible to a group of organisms that may require a different type of cultural technique for identification? Is there a skin rash that could give you a clue as to what type of organisms you might be dealing with in a systemic infection? In any case, there are two or three additional things that might be used as clues to a bacterial infection.

—ALLEN W. MATHIES, JR, MD, *Los Angeles*

Extracted from *Audio-Digest Internal Medicine*, Vol. 24, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Important Advances in Clinical Medicine

Epitomes of Progress — Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in ophthalmology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Herpes Simplex Keratitis

HERPES SIMPLEX KERATITIS is basically an epithelial disease of the cornea that might be considered the counterpart of the labial fever blister. In most cases it is a self-limited disease requiring four to ten days for spontaneous cure. Resolution of the epithelial lesions (such as dendritic ulcer) may be hastened by simple removal of the affected epithelium on a dry cotton swab or by the local use of antiviral agents such as idoxuridine, adenine arabinoside or the newly developed trifluorothymidine.

Herpetic keratitis becomes a serious problem when it involves the corneal stroma, becomes associated with iridocyclitis or when the frequency of recurrences of the epithelial lesions is so great that the patient is incapacitated for useful work. The causative virus Herpesvirus hominis has recently been shown to reside in the trigeminal ganglion between attacks. Therefore, a reservoir for the latent infection always exists within the cranium, and an outbreak of recurrent disease may be provoked at any time after the initial infection by one of a number of triggers. The commonest of these are fever, exposure to ultraviolet light, trauma and emotional stress. These triggers are important to recognize, because they may be avoided by patients subject to frequent recurrences of herpetic keratitis. The early use of aspirin in respiratory infections may prevent fever, just as the use of a broad-rimmed hat or sunglasses may prevent damage from ultraviolet exposure.

The use of corticosteroids by either local or systemic application is contraindicated in herpetic epthelial keratitis because this form of treatment may contribute to the establishment of stromal disease of the cornea and, possibly, to the invasion of deeper structures of the eye such as the uvea.

Although the initial use of corticosteroids in herpetic keratitis may whiten an otherwise red eye, the anti-inflammatory effect of the corticosteroids soon may be superseded by an immunosuppressive effect that allows for the growth of the virus in tissues upon which it does not normally propagate (corneal stroma and the like). A similar effect is seen in the absence of corticosteroid therapy among patients whose immunologic defense systems are compromised by neoplasms (for example, Hodgkin disease or multiple myeloma) or by immunosuppressive therapy that has been administered to retard the rejection of organ transplant.

Until safe and effective forms of systemic therapy for herpes simplex infections can be developed, there seems to be little likelihood that the disease will be eradicated totally. In the interval it seems wisest to administer only those forms of therapy that contribute to the local removal of the virus from the corneal epithelium and to avoid those forms of therapy that might compromise the defenses of the patient against the virus.

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Red Eye

CHRONIC LOW-GRADE INFLAMMATION of the eyelids produced by Staphylococcus aureus (staphylococcal blepharitis) is one of the most common causes of chronic ocular irritation and inflammation. Patients will complain of burning associated with a red eye. On examination of the eyelid margins there will be hard, brittle scales at the base of the eyelashes, dilated blood vessels on the lid margins and in chronic cases there can be white eyelashes or even evidence of loss of lashes. Associated findings are a chronic papillary conjunctivitis, a mucopurulent exudate containing polymorphonuclear leukocytes, inferior corneal punctate keratitis and in some cases peripheral corneal ulcers which are separated from the limbus by clear cornea. In addition, the patients may have a diminished tear secretion and recurrent hordeola.

Treatment is directed towards eliminating the organism in two ways: (1) The eyelids are scrubbed with a cotton-tipped applicator moistened in Johnson & Johnson No More Tears® baby shampoo every day for two weeks and then once a day to once a week. In addition to the shampoo, the eyelids are scrubbed with an antibiotic ointment. The following ointments are recommended: erythromycin, bacitracin and sulfacetamide. A quarter inch of the ointment is applied to a cotton-tipped applicator which is then used to scrub the eyelids at the base of the lashes a minimum of four times a day for two weeks and once a day thereafter. For severe cases, topical antibiotic drops can be used along with systemic antibiotics. Steroids are not recommended for treating this disease because elimination of the organism will eliminate the symptoms.

We most commonly think of conjunctivitis when we see patients with bilateral red eyes. In the past, most ophthalmologists thought that a clinical diagnosis could be made based on clinical evaluation of the patient and cytologic examination of the conjunctival scrapings. In addition, most workers thought that positive bacterial cultures could only be obtained in three fourths of patients cultured. It has been a surprise, therefore, to discover that the morphologic signs and usual laboratory tests are unable to produce a verified etiologic diagnosis in a large number of cases. Culturing the conjunctiva for anaerobic organisms recently has shown that the percentage of positive isolations can be increased, and it is becoming clear that anaerobic organisms are responsible for many cases of chronic conjunctivitis.

Chronic use of topical medications eventually can lead to allergic or toxic complications and misuse of these drugs by the physician or the patient can produce chronic red eyes that can be misdiagnosed as allergic conjunctivitis. Although most patients do not like to admit that they are using lubricating eye drops regularly, this history should be probed. In any patient with red eyes, studies also should be done for the possibility of decreased tear production.

When bacteria and viruses infect the cornea and produce a red eye, the cause is often obvious. More subtle causes of red eyes relating to the cornea involve the use of contact lenses. Hard contact lenses tend to produce a low-grade irritation and can produce corneal epithelial abrasions; soft contact lenses tend to adsorb protein from the tears which stimulates the production of giant cobblestone papillae over the tarsal con-

junctiva and, consequently, chronic red eyes. Cessation of contact lens wear will usually eliminate these signs and symptoms.

There are many other causes of red eye but in most instances the major ones are easy to diagnose simply by taking a careful history and examining the patient, keeping in mind the different parts of the eye and the ocular adnexa which can be involved.

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Glaucoma and Ocular Hypertension

GLAUCOMA IS A complex disease associated with increased intraocular pressure, abnormality of aqueous outflow, cupping of the optic nerve head and loss of visual field. It is generally agreed that the higher the intraocular pressure, the greater the likelihood of visual field loss. Conversely, the lower the intraocular pressure is maintained, the less likely it is that visual field loss will occur or progress.

Historically, statistics on glaucoma have been garnered by evaluation of the intraocular pressures measured with the classical Schiotz corneal indentation tonometer. Using this device, the statistical distribution of normality for intraocular pressure averages 16 mm of mercury ± 2.8 mm of mercury, with over 90 percent of persons in the normal population having intraocular pressures of less than 21 mm of mercury. Another 2.5 percent of normal persons will have pressures of greater than 21 mm of mercury and less than 0.15 percent will have intraocular pressures of greater than 24 mm of mercury. Although patients with glaucoma at times may have normal or high normal intraocular pressures, it is very uncommon for normal patients to have pressures above 24 mm of mercury.

Recently, various tonometric devices involving corneal flattening (applanation) have allowed for refinements in intraocular pressure measurements. The values of intraocular pressure in the same patient with different tonometers may vary 3 to 5 mm of mercury, depending upon the instrument used and whether the patient is examined standing or lying down. Consequently, it becomes essential to know the type of instrument utilized and the postural attitude of the patient in order to know whether he is normotensive or hypertensive. Simply stated, a 22 mm of mercury pressure with one instrument may be equivalent to a 19 mm of mercury intraocular pressure with another device.

In the most common form of glaucoma the disease is slowly developing and slowly progressive. From early laboratory evidence of disease to manifest visual field loss may take years with or without treatment. Glaucoma is an asymmetric disease, affecting the two eyes differently in the same patient. Often the pressure and field loss may vary considerably between the two eyes; or the pressure may be equivalent in the two eyes yet produce greater functional loss in one eye than the other. The concepts of normal or acceptable intraocular pressure as opposed to pathological intraocular pressure are relative ones and depend upon various factors including the patient's age, systemic blood pressure, rate of secretion of aqueous humor, chamber angle anatomy, pressure in the episcleral veins, vascular perfusion of the optic nerve and individual anatomic susceptibility of the particular optic nerve to damage. What may be a tolerable intraocular pressure for one eye may be a pathologic pressure for another.

Whether by a direct effect or by an ischemic mechanism, intraocular pressure is the culprit in a glaucomatous eye. Treatment of glaucoma involves lowering the intraocular pressure by a variety of techniques including drops, pills and surgical operation. Unfortunately, these are not without some risk (diminished visual acuity, myopia, cataracts, retinal detachments and the like). Therefore, a philosophic problem concerning therapy has arisen in the ophthalmologic community. It is a question of whether glaucoma therapy to prevent retinal and optic nerve damage should be used or therapy instituted after such damage has occurred. For cases of moderate or advanced glaucoma, treatment decisions are usually easily made. In borderline cases, decisions are more difficult and must be based on the individual case.

The term ocular hypertension has been introduced to describe persons with elevated intraocular pressure but not known (manifest) ocular damage. The term is somewhat of a misnomer because it includes some patients with high normal

intraocular pressures (21 to 24 mm of mercury) and has even been extended by some to include patients with higher pressures but no field loss or optic nerve damage.

Promotion of the term ocular hypertension has confused some physicians and many patients. It is not a unique entity, nor does it represent a class of patients resistant to abnormal intraocular pressures. Such patients should be suspected of having glaucoma, and frequently become glaucomatous. In clinical studies of persons with "ocular hypertension" the incidence of short-term field loss has ranged from 3.5 percent to 15 percent. Discriminating between ocular hypertension (frequently glaucoma at an early stage) and established chronic simple glaucoma depends upon the status of the optic disc and the visual field. Thorough and periodic examinations are a requisite to proper diagnosis and management. These patients should be followed much more carefully than the general ophthalmologic population.

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Fluorescein Angiography in Ophthalmology

FLUORESCEIN ANGIOGRAPHY has become a fairly common office test for determining the blood flow in the retina and choroid. It has been used to investigate diseases such as macular degeneration and diabetic retinopathy. The ability to determine the cause of fluid in the retina or abnormalities in the retinal vasculature has led to a better understanding of the basic pathophysiology of retinal and choroidal diseases. In turn, the understanding of these entities has led to earlier diagnosis and treatment of these debilitating, ophthalmological diseases.

Fluorescein angiography is done on an outpatient basis. Fluorescein dye (5 to 10 ml) is injected into the antecubital vein as a bolus and serial photographs are taken as the dye passes into the eye from the ophthalmic artery.

A normal fluorescein pattern is seen in Figure 1. As the timed photographs are taken, the advent of leakage from abnormal choriocapillaris areas or retinal vessel breakdowns (or both) become

Figure 1.—An angiogram showing a normal fluorescein pattern.

evident. After the choroidal flush becomes apparent, the dye enters the arterial network, which marks the beginning of the arterial phase. The lamellar flow of dye along the edges of the vein marks the beginning of the venous phase and the early venous phase is followed by more uniform filling of the veins. Any abnormal or new retinal vessels as well as old vessels which have undergone deterioration are pinpointed by leakage of the dye through the walls of the abnormal vessels. These leakage spots are pinpointed as bright, white areas of fluorescence which indicate the source of the fluid accumulation in the retina. In many cases, argon laser photocoagulation can be used to seal these areas preventing further deterioration of the retina due to accumulated fluid.

Fluorescein leakage around the optic nerve, which is found in papilledema, is an excellent way of separating cases of papilledema from pseudopapilledema caused by such entities as drusen in the optic nerve head. The test is also useful in determining the presence of ocular tumors. Retinal hemangiomas, metastatic carcinomas and malignant melanomas tend to leak large amounts of the fluorescein dye.

Reactions to the dye can be expected. The patient will have green urine as the dye is excreted by the urinary system. The skin will be slightly pale for 12 hours due to dye absorption. The most frequent complication is nausea, which will occur in about 2 percent of patients at the time the dye is injected and will last from 15 to 30 seconds. In approximately one person in

every 400 a transient rash will develop from 4 to 24 hours after injection of the dye due to allergic manifestations. One person in every 25,000 will have a major allergic reaction with syncope and cardiac problems.

Fluorescein angiography has been used more frequently in the last few years because of its low risk and high information return.

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Continuous Wear Contact Lenses

FOR NEARLY AS LONG as contact lenses have been in use, both doctors and patients have been intrigued by the possibility of continuously or permanently wearing them. Present technology and experience, as well as Food and Drug Administration (FDA) guidelines, dictate the safer and more realistic goal of prolonged or extended wear (that is, weeks or months of uninterrupted use with only periodic cleaning). For this reason, prolonged rather than permanent wear will be the focus of this epitome.

When used by a healthy, capable person for correction of vision, the convenience of prolonged wear would be a tremendous boon. For most elderly aphakic persons, convenience is superseded by near necessity. After cataract extraction the visual difficulties encountered by patients wearing spectacles are well documented. The use of extended wear contact lenses and their associated risks are more easily justified in these patients. Prolonged wear frees elderly aphakic patients from the often incapacitating visual adjustment to glasses and from the need to master the difficult techniques of insertion and removal of regular contact lenses. Many of these patients who have no ophthalmic contraindications to wearing conventional contact lenses are, however, handicapped by deformities, tremor or reduced digital dexterity. Sadly enough, they even have difficulty seeing the lenses.

The major impediment to prolonged wear has been corneal hypoxia. Hypoxia, directly or indirectly, leads to a number of complications including corneal edema, sloughing of the corneal epithelium (the extremely painful overwearing syndrome), increased susceptibility to corneal infection and corneal neovascularization which can interfere with vision.

Actually, modified prolonged wear lenses have been used for more than 20 years by a small number of patients fitted with conventional non-gas permeable "hard" plastic contact lenses. During the waking (eyes open) hours, a properly fitted lens and a good blink reflex allow adequate dissolved oxygen to reach the cornea via the tears. Spontaneous nightly movement of the lens off the cornea and onto the sclera by the patient circumvents the problem of corneal oxygen starvation that exists during sleep with the hypoxic combination of lens in place, closed lids and minimal tear exchange. Some patients can even tolerate very small and thin contact lenses on their corneas without removal.

With the hope of producing a more physiologic prolonged wear device, manufacturers have developed new materials which would provide better corneal oxygenation with the lens left in place during sleep. One such innovation is the "soft" hydrophilic contact lens with its moderate oxygen permeability. These lenses allow adequate oxygenation in the eyes open state, but borderline hypoxia when the lids are closed. Considerable data from the last eight or ten years indicate the relative safety of continuously worn therapeutic hydrophilic lenses. These have been used primarily in the treatment of existing corneal disease. Reported complications of prolonged use include conjunctivitis, corneal edema, corneal opacity formation, infectious corneal ulcers and neovascularization. The magnitude of these difficulties is low enough to justify prolonged wearing in a therapeutic situation.

Recently, both hard and soft contact lens devices with high oxygen flux have been developed specifically for prolonged wear in normal eyes for vision correction. Investigators using these newer lenses in Canada, England, Europe and Japan report encouraging results with few complications. Case studies indicate that 60 percent to 70 percent of well-selected patients can wear these contact lenses for prolonged periods, with cleaning every few months. Long-term, controlled data are not yet available to support these claims.

In the United States, *no* prolonged wear contact lenses are FDA approved for vision correction, although therapeutic fitting is allowed. A num-

ber of manufacturers have started investigations, under strict FDA supervision, to test the efficacy and safety of prolonged-wear contact lenses. A minimum two-year study period will be required before the FDA determines the acceptability of various contact lenses for prolonged cosmetic and visual wear.

Until the real risks of prolonged wear contact lenses are known, both patients and doctors would be advised to adopt a conservative wait-and-see attitude. Most investigators in the field, however, are confident that safe prolonged wear contact lenses are a realistic possibility for the future.

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EDITORIALS

Participatory Democracy and Health Care

It was only a decade or so ago when the government planners for health care seemed to be firmly in the saddle. It seemed to be a heyday for attempting to find national solutions to national social problems, including health care. Equal access to the vote, affirmed by the famous one man one vote decision of the United States Supreme Court, strengthened the expectations of many for equal access to everything else, and again this included health care. The now all too familiar series of federal "initiatives," as the government likes to call them, came into being and continue until this day. For a while it appeared that the majority, led by federal planners who had in mind what they thought would be best for everybody, might ride roughshod over those with minority views, or even over an individual person's right to be different or to place a different value on what might be best for him or her. There was comparatively little direct public participation in planning or the decision making processes. But this was more than a decade ago.

In the late 1960's a countervailing force came upon the scene. A deep and widespread revolt against authority developed among college students and the younger generation which was reaching maturity at that time. They declined to be passively absorbed into the establishment, emphasized their right to be different and to find their own individual personal fulfillment in their own way. They espoused the causes of minorities of all kinds and demanded to be part of planning and decisions which affected them. At first the effects of this were upon colleges and universities, and they were profound. But now its impact is beginning to be felt in many other aspects of today's society. In health care, for example, a physician's authority is much less likely to be taken at face value, the effectiveness of much that was thought to be scientific medicine is being questioned, and we are beginning to see a substantial interest in many alternative and less scientific methods of care and treatment which would have received scant attention as recently as the early 1960's.

It would seem, therefore, that two things are happening. The federal initiatives in health have not been as effective as the planners had expected and the impetus for centralized federal control of health care is diminishing as the costs rise, while the public demand for more direct participation in planning and decisions which affect them is increasing substantially. If these trends continue, and they continue to focus on health care as seems likely, a new era of participatory democracy for planning and decision making in this field may be beginning. Indeed this seems to be the case. Informed consent already has made participatory democracy a reality in the care of patients, and the Health System Agencies (HSA's) are now making it a reality for planning and decision making for health and health care for local communities.

All of this suggests an important change in the ways physicians can be most effective. Instead of giving orders on the assumption they will be followed or making public pronouncements on the presumption that they will be accepted without question, it is now becoming necessary for physicians to bring their professional expertise to bear in other ways. However, what is needed is really nothing new. Rather it foreshadows a renaissance and a further refinement of the age-old function of physicians to help and to teach. Physicians can uniquely give authoritative information about health and its disorders; what is wrong, what is likely to happen and what can be done about it. And when they act as consultants, advisers and teachers—whether of patients or the public generally—they can be effective indeed as peer par-

ticipants in the planning and decisions for health care at the patient, community or national level. It now behooves physicians and the medical profession to spend the time necessary and develop the skills needed to participate fully in this new participatory democracy which has become such an important part of medicine and health care in the society we serve.

—MSMW

Adult Respiratory Distress Syndrome

What To Do Until the Basic Scientist Comes

THE CLINICAL MANIFESTATIONS of diffuse injury to the lung parenchyma vary from fulminant pulmonary edema that may be rapidly fatal to the much more indolent pulmonary fibrosis causing chronic abnormalities of gas exchange, disability and death in some cases. The determinants of the response of the lung to a given injury are unknown and, perhaps more important, the mechanisms by which the injury is delivered are obscure. However, in the past eight to ten years there has been considerable elucidation and definition of the effects of the acute form of lung injury on pulmonary function, and as a consequence of this understanding, more effective approaches to therapy have been developed.

The review of what, for want of a better term, is called the adult respiratory distress syndrome (ARDS) by Petty and Newman in this issue of the WESTERN JOURNAL discusses the development of concepts regarding this form of respiratory failure and presents current ideas as to pathogenesis, prevention and treatment. As with other reviews[1,2] of the topic, the present article raises more questions than it answers (an important function of a review article).

One of the more important current questions concerns terminology. The obvious imprecision of the designation ARDS has been discussed previously.[3,4] As noted by Petty and Newman, the lack of general acceptance of this term is apparent by the extraordinary number of synonyms used. Because of a lack of accepted, precisely defined terminology, it is difficult to develop information concerning incidence, natural history and response to therapy. Cooperative studies that attempt to examine any but the most flagrant examples of this form of respiratory insufficiency are doomed to failure because of the inability to define adequately what constitutes the study population. Nevertheless, the catchall term ARDS has been used widely and frequently enough so that it does, in the minds of most physicians, conjure an image of a form of respiratory failure that is quite different from the other common form of respiratory failure—that caused by airway obstruction. For this reason the continued use of the term is of some value, assuming that when specific causes are identified, they will be removed from the ARDS "wastebasket" and treated as separate entities. A good analogy is the clinical and pathophysiologic complex called "heart failure." A diagnostic evaluation does not end when it is determined that heart failure is present; there is an obligation to find the cause of the heart failure by as complete an examination as is necessary and available. The same philosophy should apply to the patient who is considered to have ARDS.

A whole set of complicated interrelated questions concerning prevention and treatment derive from our lack of knowledge concerning basic mechanisms of injury. It is obvious from reading the "Theories of Pathogenesis" section, and Table 3, in the Petty-Newman paper that many mechanisms alone or in combination are involved. Were we able to identify specific mechanisms in individual patients, then specific therapy could be applied. Theoretic arguments can be raised for the use of corticosteroids and heparin as well as several other agents. However, it has yet to be shown convincingly that any of these compounds has a beneficial effect in patients with ARDS. Here, the problems of imprecise terminology and lack of knowledge of basic mechanisms pose major stumbling blocks. The mechanisms by which acute lung injury occurs were the subject of a recent National Heart, Lung, and Blood Institute workshop that was designed to identify specific research needs.[5] Although the direction provided by this workshop, as well as research currently underway in many centers, certainly holds promise, it appears that we are still several years away from clinically applicable information concerning basic mechanisms. Therefore, for the time being we must be content to treat with supportive rather than curative measures.

We do know that once the lung injury has occurred, the ensuing sequence of events is quite similar regardless of the cause. As Petty and New-

man state, there is considerable evidence indicating that the injury exerts its effect by increasing the permeability of the pulmonary capillary endothelium, thereby allowing fluid to escape initially into the interstitial space and subsequently into alveoli. The increase in pulmonary capillary permeability grossly alters the relationships of the forces that govern fluid movement across the capillary wall. Under these conditions, any increase in the hydrostatic pressure within the capillary causes more fluid to escape from the capillary. Consequently, the fluid management of patients who either have ARDS or are at risk of ARDS developing is of critical importance. Fluids should be carefully administered keeping clear-cut end points in mind, the volume administered being just sufficient to restore or maintain critical organ perfusion with as little increase as possible on the pulmonary capillary (wedge) pressure. (The house staff at San Francisco General Hospital Medical Center have accused us of forcing them to "sneak in at night" to give their patients fluids. We do not deny the accusation.) It should be emphasized that as a guide to fluid replacement in this situation, measurements of central venous pressure are inadequate and frequently misleading. Measurements of cardiac output and pulmonary artery wedge pressure provide much more immediate and accurate information on the need for and effects of fluid administration. However, in many hospitals these are not readily available; therefore, one should rely on other indexes of the state of perfusion including urine output, skin temperature, central nervous system function, blood pH and blood lactate concentrations.

Our current understanding of the pathophysiology of ARDS provides another important approach to prevention and treatment. This is the use of continuous positive pressure ventilation (CPPV). There are more than ample data to document the usefulness of this pattern of mechanical ventilation in patients who have ARDS. Continuous positive pressure ventilation exerts its effect by increasing the volume of gas in partially inflated alveoli or by reinflating collapsed alveoli (or both). Again, by an analysis of the forces acting across the capillary wall it seems logical that early intervention with mechanical ventilation using CPPV may be of some preventive value by lessening the effect of a given injury. By maintaining alveolar inflation, intraalveolar surface tension is reduced. This should lessen the negativity of the hydrostatic pressure in the pericapillary interstitial space and thereby decrease the pressure gradient between capillary and interstitium. Such a prophylactic effect of CPPV is suggested by two studies showing that in animals ventilated with high tidal volumes the addition of positive end expiratory pressure tends to conserve surfactant and thereby reduces alveolar surface forces[6] and also prevents pulmonary edema.[7]

Although there are still many unanswered questions concerning acute pulmonary injuries, there is at our disposal sufficient information to guide effective supportive care. In addition, there are many situations in which one can anticipate the risks of ARDS and apply the principles of supportive care in a preventive fashion. We await with eager anticipation the revelations that will allow the application of specific curative measures.

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Medicine in Ponape

THE EXPERIENCE of a medical resident in Ponape described elsewhere in this issue serves to draw attention to the sharp differences between medical practice where all the modern resources are available and where they are not. It also emphasizes what it may take to make them available and used appropriately in medically backward areas.

Some similarities between medical practice in the United States and in Ponape stand out with clarity. Patients do not always volunteer all the appropriate information. They may not understand what a physician is asking them or telling them. Cultural attitudes and beliefs may be as

important in patient care in the United States as in its trust territories. And clinical acumen remains a sine qua non to be cultivated by every doctor no matter what the specialty or where the practice.

Medicine in Ponape in many ways may be backward but it can teach something not only to a medical resident, but to physicians everywhere.

—MSMW

Management of Asthma

ASTHMA has been defined as "recurrent episodes of wheezing or dyspnea characterized by a significant increase in resistance to air flow. Spontaneously or following treatment, periods of complete or almost complete freedom from symptoms occur accompanied by a substantial decrease in resistance to air flow."[1]

Therefore, today we recognize that asthma is a complex group of symptoms and signs caused by one or several mechanisms and triggered by many factors. Spector and associates[2] describe subdivisions of asthma based primarily upon responses to various modes of treatment. A classic, and I think still useful, subdivision is intrinsic, extrinsic and mixed asthma.

Intrinsic asthma refers to reversible bronchospasm usually with infections that occur in nonatopic persons with no family or personal history of allergy and negative findings on skin tests and other immunologic and physiologic tests with specific allergens. The onset of intrinsic asthma commonly occurs in adulthood and the category includes most adults who have asthma.

Extrinsic asthma most commonly occurs in children, usually associated with other allergies, rhinitis, eczema, serous otitis, gastrointestinal symptoms, a positive family history of allergy or positive skin and other tests with specific allergens.

Mixed asthma refers to reversible bronchospasm that occurs in atopic persons but is unassociated with specific allergens. Obviously, there is much overlap among these groups, but the divisions are useful in anticipating possible responsiveness to therapeutic measures.

The first approach to a patient with asthma is to determine whether atopy and specific allergens are involved. The history of attack onset upon inhalation or ingestion of specific allergens, family or personal history of other allergies, and exposure to common known allergens should provide an index of suspicion that may be confirmed by skin and laboratory tests. If a test of total serum IgE, as described by Hamburger in this month's Specialty Conference, shows an elevated level, this serves to confirm atopy although one must recognize that IgE antibody against a specific antigen is of primary importance. Indeed, an atopic asthmatic person may have normal total serum IgE level and a notably elevated IgE-RAST* to a specific allergen. Furthermore, serum IgE antibody titer per se is merely a mirror of shock organ target tissue IgE antibody which, although currently not measurable, determines allergic status because the allergic reaction occurs in this tissue. The ultimate proof that an allergen causes asthma is by allergen inhalation or ingestant provocation of measurable symptoms or signs, for example, a 15 percent drop in forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR).

In such an asthmatic patient, removal of all the inciting allergenic inhalants or ingestants by environmental control or elimination diet, respectively, should be successful in controlling symptoms. Great success has resulted from the removal of a pet dog or cat from the home of such a sensitive person. Furthermore, no amount of other therapy is successful if the offending allergen is not removed. Rackemann[3] reviewed his 20 years of practice experience and cited failure to insist on removal of a pet animal in the case of a dander allergic asthmatic patient as the chief cause of failure in treatment of asthmatics. Where complete removal of the allergen is impossible (as with pollens, molds and house dust mite), altering the patient's immune status with immunotherapy may be successful. Because the clinical course of asthma by definition is reversible, it is most difficult to evaluate long-term treatment such as immunotherapy on a double-blind basis to show a statistically significant improvement. Lichtenstein[4] recently outlined these difficulties. However, D'Souza and co-workers[5] did show statistically significant improvement ($p<0.05$) of wheezing and cough, drug use and inhalation tolerance to dust in a group of 45 house dust sensitive asthmatic persons undergoing immuno-

*RAST stands for radioallergen sorbent tests. Antigen is coupled to a solid phase immunosorbent and reacted with serum from an allergic person with IgE antibodies to the antigen. This complex is reacted with radio-labeled anti-IgE and centrifuged. Radioactivity measured in the washed pellet indicates amount of IgE antibody to that antigen.

therapy with mite (Dermatophagoides pteronyssinus) extracts, compared with 46 such patients receiving placebo injections.

Cromolyn sodium apparently prevents the release of mediators (for example, histamine and slow-reacting substance of anaphylaxis) from mast cells and basophils resulting from IgE-antibody mediated reactions. This agent is a successful preventive drug in managing a large number of extrinsic asthmatic children.

Allergy to foods continues to be a subject of much controversy. Immediate anaphylaxis to foods is incontrovertible. However, the role of foods in inducing asthma runs the gamut from complete denial[6] to almost universal causation.[7] IgE-mediated food allergy can be documented by history, prick skin tests, leukocyte histamine release[8] and RAST.[9] However, some patients are relieved of asthma by a specific food elimination diet, despite negative findings on IgE-antibody tests. This suggests other immune mechanisms, such as immune complexes which may possibly liberate anaphylatoxins C_3a and C_5a to cause mast cell histamine release which initiates asthmatic symptoms.

Asthmatic patients, both extrinsic and intrinsic, have irritable airways so that minute doses of inhaled irritants, such as sulfur dioxide and methacholine, cause bronchospasm; similar inhaled doses have no effect on nonasthmatic persons. An imbalance in the autonomic nervous homeostatic controls of bronchial smooth muscle tone in asthma has been postulated by Szentivanyi.[10] Impaired adenylate cyclase responsiveness to β-adrenergic agonists in leukocytes of asthmatic persons has been shown.[11] Others[12] suggest a cholinergic overresponsiveness in asthma. Release of mediators from mast cells is also under similar cyclic nucleotide controls. Histamine release is inhibited by cyclic adenosine monophosphate (cyclic AMP) and enhanced by cyclic guanosine monophosphate (cyclic GMP). Therefore, pharmacological approaches to asthma are directed at correction of this imbalance by increasing cyclic AMP with β-agonists, especially those with primarily β_2 receptor activity, in smooth muscles and mast cells or blocking the breakdown of cyclic AMP by phosphodiesterase with theophylline.[13]

In this month's Specialty Conference, Mellon and co-workers review the newer developments with drugs. Monitoring of plasma theophylline concentrations and the development of long-acting oral theophylline preparations has permitted higher doses to be administered on a round-the-clock basis to maintain an effective therapeutic blood level of 10 to 20 μg per ml.[14] The considerable patient variation in theophylline catabolism, especially in children, makes tailoring of theophylline dosage to the individual patient desirable. It is also becoming apparent that a particular patient's theophylline catabolism may vary, especially during an asthmatic attack with dehydration.

Several new β_2-adrenergic agonists (terbutaline, salbutamol, fenoteral) that relax bronchial smooth muscle with little, if any cardiac effect, are being promoted as specific for asthma. They are, indeed, effective in decreasing bronchospasm, as evidenced by reduced airway resistance measurements.[15] However, the pathology of asthma in addition to bronchial smooth muscle spasm, has components of mucosal edema and increased or changed mucus secretion. As the vascular effect of the β_2 agonists is minimal, correction of mucosal edema may be less effective with these new drugs. Their effect on mucus secretion is also under study. For this reason, drugs with some β_1- or α-adrenergic action, like ephedrine and metaproterenol, may still be preferred in some patients. Finally, skeletal muscle tremor is a β_2-adrenergic property and can be troublesome for patients receiving these agents, although this may wane with continued use. The synergistic action of theophylline and β-agonists on cyclic AMP has been the basis for fixed drug combinations for asthma therapy for many years. Current fashion is to take advantage of this synergy and tailor individual drug doses for a particular patient using the new β_2-agonists and theophylline.

Cromolyn sodium apparently stabilizes the mast cell membrane to prevent release of mediators in antigen-IgE-induced asthma. However, cromolyn sodium has been found to be effective in certain patients with intrinsic infectious asthma and in cases of exercise-induced asthma.[16] Therefore, the mechanism involved in these forms of asthma and all the actions of cromolyn are not yet clear. It is conceivable that infectious asthma is mediated by IgE or IgG antibodies to bacteria or viruses and via the complement-activated anaphylatoxins, in which case cromolyn might still act primarily on mast cells to prevent histamine release.

The newest major therapeutic development is inhaled topical corticosteroids, such as beclo-

methasone dipropionate, triamcinolone acetonide, fluocinolone. These have proven quite effective in managing chronic steroid dependent asthmatic patients, in whom it has been possible to reduce or eliminate systemic corticosteroids in most cases.[17] The Food and Drug Administration has approved the release of beclomethasone dipropionate:

> only for patients who require chronic treatment with corticosteroids for control of symptoms of bronchial asthma. Such patients would include those already receiving systemic corticosteroids, and selected patients who are inadequately controlled on a non-steroid regimen and in whom steroid therapy has been withheld because of concern over potential side effects.[18]

However, it is common practice today simply to give inhaled topical steroid a trial first in patients with moderate asthma before trying other, more extensive workups to eliminate allergens and use of other drugs. We believe that this is a dangerous practice because oral and pulmonary candidiasis have been observed in such patients and the long-term effect of continuous topical corticosteroids on airways is unknown. Chronic topical steroid use on the skin produces a pronounced thinning of the epidermis, which may lead to increased infections and risks of contact sensitization. In patients who have been receiving systemic corticosteroid, the switch to inhaled topical steroids may be accompanied by adrenal insufficiency and failure at times of infectious or surgical stress, if administration of supplemental systemic steroid is forgotten. Also, nonrespiratory symptoms, such as eczema, may become worse.

Optimal management of asthma involves identification of potential allergens and trigger mechanisms and eliminating or controlling them, followed by supplemental immunotherapy, if appropriate, and pharmacological management or prevention of asthmatic symptoms to permit patients to lead as normal a life as possible.

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CASE REPORTS

Refer to: Miser JS, Robertson WO: Ipecac poisoning. West J Med 128:440-443, May 1978

Ipecac Poisoning

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THE USE OF syrup of ipecac in managing accidental ingestions of drugs in children is now widely recommended. Dabbous and co-workers[1] showed that the syrup of ipecac was more effective than mechanically induced vomiting; other authors have shown ipecac to be more effective than gastric lavage.[2,3] Because delay in gastric evacuation is directly related to increased drug absorption, syrup of ipecac is presently recommended for use in the home, thereby avoiding the delays of transit to the hospital. The usual therapeutic dose for children is 15 to 30 ml; it may be repeated in 20 to 30 minutes if emesis has not occurred. At this dose, syrup of ipecac is safe in the treatment of acute ingestions. In contrast the fluid extract form of ipecac is 14 times as concentrated as the syrup form and its use has been associated with severe toxicity and fatalities. For this reason fluid extract of ipecac was removed from the *United States Pharmacopoeia* in the mid-1960's. Nonetheless, we have recently seen a three-year-old child who became ill after ingesting fluid extract of ipecac administered inadvertently in treating an accidental ingestion of propoxyphene napsylate (Darvon-N®).

Report of a Case

A three-year-old black boy was admitted to the Children's Orthopedic Hospital and Medical Center in Seattle in status epilepticus. Except for an episode one year before admission of a temperature of 40.6°C (105°F) associated with seizure activity, the child's past medical history was normal. A subsequent electroencephalogram showed no abnormalities and anticonvulsant therapy had not been instituted. The patient was well until the evening before admission when he ingested three 100-mg tablets of propoxyphene napsylate. Upon discovery of powder on his face and an open medication container, his mother called the Poison Control Center at the Children's Orthopedic Hospital and was instructed (1) to obtain syrup of ipecac as quickly as possible, (2) to administer one tablespoon of the syrup to the patient followed by water and (3) to repeat the dose once if vomiting had not commenced in 15 to 20 minutes. The child's 12-year-old cousin was sent to a local pharmacy for the syrup of ipecac. The pharmacist had no small bottles of syrup of ipecac, but he did have a half-filled old brown bottle labeled "Ipecac," which he sold to the cousin. One tablespoon of the bottle's content was administered to the patient. When the child failed to vomit in 20 minutes, a second tablespoon was almost administered, but the patient refused the offering and soon began to vomit. He continued to vomit throughout the next 12 hours and 6 hours before admission profuse watery diarrhea developed. One hour before admission, opisthotonic generalized convulsions occurred.

After control of the seizure an initial physical examination was carried out. The child was moderately alert; tachypnea was noted. The pulse rate was 140 beats per minute; respirations, 35 per minute; blood pressure, 110/80 mm of mercury, and temperature, 38.7°C (101.7°F). The skin was dry with some tenting but the mucous membranes were moist. There was erythema of the posterior pharyngeal mucosa. Examination of the heart and lungs gave normal findings except for tachycardia and tachypnea. Examination of the abdomen showed generalized tenderness without guarding or rebound tenderness; bowel tones were normal. The remainder of the physical examination showed no abnormalities.

Laboratory studies gave the following findings: hematocrit, 46 percent; leukocyte count, 45,800 per cu mm with increased immature polymorphonuclear leukocytes with toxic granulation and vacuolization; platelet count, adequate; serum sodium, 153 mEq per liter; potassium, 4.5 mEq per liter; chloride, 119 mEq per liter; bicarbon-

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Submitted November 18, 1977.

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ate, 9 mEq per liter; blood glucose, 3 mg per dl; blood urea nitrogen, 42 mg per dl; arterial oxygen pressure, 75 mm of mercury; carbon dioxide pressure, 27 mm of mercury; pH, 7.32; serum glutamic oxaloacetic transaminase, 47 IU, and serum glutamic pyruvic transaminase, 12 IU. Cultures of urine, stool, blood, and cerebrospinal fluid specimens all proved negative. Stool was guaiac positive. An x-ray film of the chest showed no abnormalities; air fluid levels in the small bowel lumen were seen on films of the abdomen.

The patient was treated first with intravenously given glucose and phenobarbital at a dose of 5 mg per kg of body weight per day; an electroencephalogram made six days later showed diffuse slowing. Watery diarrhea persisted for ten days; however, fluid and electrolyte status improved over the first three days in hospital. An upper gastrointestinal series of roentgenograms gave normal findings and sigmoidoscopy showed diffuse colitis. During his hospital course other abnormalities were noted: T wave inversion on an electrocardiogram, muscle tenderness with mild weakness, transaminasemia, hypoalbuminemia, an initial leukocytosis and granulocytosis followed by neutropenia with a granulocyte count of 950 per cu mm, pseudo-Pelger-Huet cells, thrombocytopenia with a platelet count of 40,000 per cu mm and anemia with a hematocrit reading of 28 percent. Bone marrow examination showed vacuolization of the myeloid percursors, hyperpyknosis and hypersegmentation of the nuclei of the neutrophils, mild hypoplasia of the erythroid series, and normal megakaryocytes.

After two days in hospital the unwitting substitution of the fluid extract of ipecac for the syrup of ipecac was discovered. With careful monitoring and supportive care all signs, symptoms, and abnormal laboratory findings resolved and the child was discharged after two and a half weeks in hospital. Follow-up examinations have shown normal growth, normal development, and normal hematologic profiles.

After the discovery of the substitution of the fluid extract for the syrup, the local pharmacy, the state board of pharmacy and the National Clearinghouse of Poison Control Centers were notified.

Discussion

The first reported case of poisoning due to ipecac was published in 1908 by Harrison.[4] The physician's stable boy had pilfered and consumed the fluid extract of ipecac, which caused uncontrollable vomiting and death. Since that time 12 more cases of ipecac poisoning have been reported, 9 due to the fluid extract form and 3 due to the syrup form. Although Thoman and Verhulst[5] reported syrup of ipecac safe and efficacious in acute phenothiazine poisoning, all three of the cases of poisoning due to the syrup of ipecac occurred following previous phenothiazine overdoses, drugs known for their antiemetic properties. In each case there was evidence of cardiac toxicity. Two of these cases were not reported in detail;[6] in the third case there was evidence of atrial irritability and T wave inversion.[7]

The remaining nine cases were due to the ingestion of the fluid extract of ipecac, which resulted in four deaths and severe toxicity (see Table 1) including protracted vomiting and diarrhea; gastrointestinal bleeding and ulceration; esophageal stricture; fluid and electrolyte abnormalities; pneumonia; cardiac toxicity consisting mainly of tachycardia, atrial irritability and ST-T wave abnormalities on electrocardiograms; hematologic abnormalities involving all cell lines; and seizures. The effects of ipecac are the result of its main contents, cephaline and emetine, though they may also be due to psychotrine, hydroipecamine and ipecamine—other alkaloids present in small amounts.

In our patient many of these reported toxic effects were seen. He presented in status epilepticus and was noted at the same time to be hypoglycemic. Emetine has been reported *in vitro* to inhibit glycogen synthesis and gluconeogenesis.[8] *In vivo* studies in rats have shown decreased liver glycogen stores in emetine-treated rats.[8] Bates and Grunwaldt's[9] second patient had seizures which stopped when glucose was administered, suggesting that hypoglycemia may have been a cause of seizures. In our patient convulsions stopped after intravenous administration of glucose and an anticonvulsant. As occurred in our patient, diarrhea and vomiting have been reported in all the cases of poisoning due to the fluid extract of ipecac. In 11 of the 14 patients some cardiac toxicity was noted; in our patient only T wave changes on electrocardiograms were noted. Goodman and Gilman[10] state that neuromuscular aching, tenderness and stiffness of skeletal muscles may occur as a result of emetine ingestion. In our patient exquisitely tender skeletal muscles developed, a symptom that resolved slowly over

TABLE 1.—*Clinical Manifestations of Ipecac Poisoning*

Case	Author	Date	Age	Fluid or Syrup	Ingestion Caused Death	Gastrointestinal	Cardiovascular System	Nervous System	Other
1.	Harrison RT[4]	1908	20 years	Fluid	yes	Vomiting	Rapid pulse	.....	.....
2.	Allport RB[11]	1959	2½ years	Fluid	no	Vomiting, melena	ST-T wave changes	Seizures	Leukopenia, esophageal stricture
3.	Smith RP et al[13]	1961	4 years	Fluid	yes	Vomiting, diarrhea	Shock	Confusion	Renal damage
4.	Bates T et al[9]	1961	4 years	Fluid	yes	Vomiting	ST-T wave changes	.....	Hematologic, hematuria
5.	.....	1961	34 months	Fluid	no	Vomiting, diarrhea	None	Seizures	Leukocytosis
6.	MacLeod J[7]	1963	23 months	Syrup	no	None	T wave abnormalities	.....	.....
7.	Speer JD et al[12]	1963	3½ years	Fluid	no	Vomiting	None	.....	.....
8.	.....	1963	3 years	Fluid	yes	Vomiting, gastro-intestinal bleeding	ST-T wave changes	Seizures, apnea	Leukocytosis, renal damage
9.	.....	1963	2½ years	Fluid	no	Vomiting, gastro-intestinal bleeding	None	.....	.....
10.	Bourianoff G[6]	1971	....	Syrup	no	None	Yes	.....	.....
11.	.....	1971	....	Syrup	no	None	Yes	.....	.....
12.	Rose NJ[14]	1970	19 months	Fluid	yes	Diarrhea	Shock	Seizures, lethargy	.....
13.	Manno B et al[15]	1977	7 months	Fluid	no	Vomiting, diarrhea	Tachycardia	.....	.....
14.	Miser JS et al	1978	3 years	Fluid	no	Vomiting, diarrhea	T wave changes	Seizures	Hematologic, hypoglycemia, muscle tenderness

one month. Several authors have reported hematologic effects[9,11,12] of ipecac toxicity. We observed an initial leukocytosis and then a pronounced neutropenia, reticulocytopenia, anemia and thrombocytopenia which resolved gradually over one month. Bone marrow examination showed pseudo-Pelger-Huet cells, toxic granulation and vacuolization of the granulocyte series, mild erythroid hypoplasia and a normal megakaryocyte series.

Investigation of the inadvertent drug substitution uncovered the facts that the bottle of fluid extract of ipecac had been manufactured in 1959 and distributed by a wholesaler shortly thereafter. It had been reshelved by the retailer in the mid-1960's and, purportedly, the dispensing pharmacist was unaware of any difference in the potential toxicities of the two forms. Subsequently professional efforts were initiated to eliminate a repetition of this unfortunate occurrence by notification of all pharmacies throughout the state of Washington.

It is important to note that there are strikingly few cases of toxicity due to the syrup of ipecac considering that it is now widely used in the treatment of acute drug ingestion. It is necessary for the health care system to institute "fail-safe" mechanisms to avoid all forms of error in drug therapy. Continuous monitoring by public agencies, professional organizations and individual health professionals is mandatory in our increasingly complex chemical environment.

Summary

We report a case of poisoning due to the unwitting substitution of fluid extract of ipecac for syrup of ipecac in the management of acute propoxyphene napsylate (Darvon®) ingestion. We also review the reports in the literature of ipecac poisoning and summarize the clinical manifestations; they include protracted vomiting, diarrhea, gastrointestinal bleeding and ulceration, esophageal stricture, fluid and electrolyte abnormalities, cardiac toxicity, hematologic toxicity, seizures, hypoglycemia, muscle tenderness, shock and death.

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Refer to: Nusser RA, Tarkoff MP: Legionnaires disease causing adult respiratory distress syndrome—Survival and report of open lung biopsy. West J Med 128:443-448, May 1978

Legionnaires Disease Causing Adult Respiratory Distress Syndrome

Survival and Report of Open Lung Biopsy

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LEGIONNAIRES DISEASE may result in a fulminant pneumonia. This disease occurs in both epidemic and sporadic cases. No doubt this entity is more common than was previously recognized. We successfully treated a patient in whom adult respiratory distress syndrome developed secondary to Legionnaires disease. The purpose of this report is to detail the clinical features of this case and review an open lung biopsy study done four days after hospital admission. We are not aware of previous lung biopsies done in cases of this disease. The biopsy study showed pronounced leukocytic infiltration, edema fluid and hyaline membranes. Legionnaires disease should be considered in differential diagnosis of adult respiratory distress syndrome especially if there are leukocytic histologic features.

Hyponatremia present on admission was due to inappropriate secretion of antidiuretic hormone.

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Submitted November 16, 1977.
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Figure 1.—X-ray film of the chest made on admission showing right upper lobe pneumonia.

Pulmonary function tests following discharge returned to normal. A mild relapse occurred one week following discharge.

Report of a Case

A 58-year-old white man was admitted to Samuel Merritt Hospital, Oakland, with a chief complaint of high fever. He had been in his usual state of health until three days before admission, when malaise began. Two days before admission, nausea and retching occurred. On the morning of admission his temperature was 40°C (104°F) and an x-ray study of the chest (Figure 1) showed wedge-shaped alveolar infiltrate in the right upper lobe. The patient had noted no respiratory symptoms; specifically no cough, sputum production, chest pain, dyspnea, wheezing, sore throat or coryza. He said that diarrhea, frequency or dysuria had not been present.

A diagnosis of multiple sclerosis had been made 25 years earlier but this condition had never caused any significant problems. He had smoked one pack of cigarettes per day for the past 40 years.

On physical examination at admission, blood pressure was 140/80 mm of mercury; pulse, 92 per minute; respirations, 18 per minute, and

Figure 2.—X-ray film of the chest made on the third day showing progression of pneumonia on right and spread to left middle and lower lung fields.

Figure 3.—Chest on fourth day showing "white out" of both lungs.

temperature, 40.3°C (104.6°F). There were a few rales in the right chest. There were no other positive findings.

Initial laboratory studies gave the following values: hemoglobin, 13.1 grams per dl; leukocyte count, 11,000 with 91 percent neutrophils, 5 percent lymphocytes, 4 percent monocytes; sodium, 124 mEq per liter; potassium, 4.2 mEq per liter; blood urea nitrogen, 12 mg per dl; creatinine, 0.9 mg per dl; serum glutamicoxalacetic transaminase, 53 U (upper limit of normal, 35 U). Arterial blood gas studies, on room air showed a pH of 7.51, a carbon dioxide pressure (Pco_2) of 24 mm of mercury, and an oxygen pressure (Po_2) of 65 mm of mercury. Findings on analysis of urine were unremarkable. Initial sputum Gram stain showed only rare leukocytes and no organisms. Culture subsequently grew no pathogens.

Hospital Course

The admitting diagnosis was viral pneumonia. However, after all the cultures were obtained treatment was instituted with 1 million units of penicillin given intravenously every six hours. The serum osmolality was 215 mOsm per liter, with urine sodium of 27 mEq per liter. A simultaneous urine osmolality was 680 mOsm per liter which confirmed the diagnosis of inappropriate antidiuretic hormone secretion. The patient was treated with fluid restriction.

On the third day an x-ray film of the chest (Figure 2) showed increased infiltrate in the right upper lobe and a new infiltrate in the left lower lobe. Body temperature remained at 40°C (104°F). For the first time he complained of dyspnea. The penicillin was stopped and parenteral methicillin therapy (1 gram every six hours) and gentamycin administration (80 mg every eight hours) were started empirically. All cultures remained negative. Sputum production remained minimal and findings on Gram stain again were unremarkable. The leukocyte count was 7,800 with 52 segmented neutrophils and 44 bands. Skin tests for tuberculosis and coccidioidomycosis were negative. An antinuclear antibody study was negative.

On the fourth hospital day, x-ray films of the chest showed both lung fields were opacified (Figure 3); and the patient was in pronounced respiratory distress. Intubation was carried out and assisted ventilation begun. Arterial blood gas studies on inspired oxygen concentration of 100 percent showed a pH of 7.41, Pco_2 of 25 mm of mercury, and Po_2 of 150 mm of mercury. Later that evening he became hypotensive and a dopamine drip was started. A Swan-Ganz catheter was inserted and the pressures were as follows: right ventricle, 30/0 mm of mercury, pulmonary artery, 30/12 mm of mercury with a mean of 19 mm of mercury; pulmonary artery wedge, 10 mm of mercury. Treatment was carried out with an in-

fusion of salt poor albumin, furosemide (Lasex®), digitalis and 1 gram of methylprednisolone. Positive and expiratory pressure (PEEP) was added. However, the alveolar-arterial oxygen gradient continued to widen.

On the morning of the fifth hospital day, blood gas studies showed a pH of 7.44, P_{CO_2} of 20 mm of mercury and P_{O_2} of 55 mm of mercury on inspired oxygen concentration of 100 percent and PEEP of 15 cm of water. This further deterioration occurred despite the fact the wedge pressure remained below 10 mm of mercury at all times. However, the patient's blood pressure stabilized and dopamine administration was discontinued.

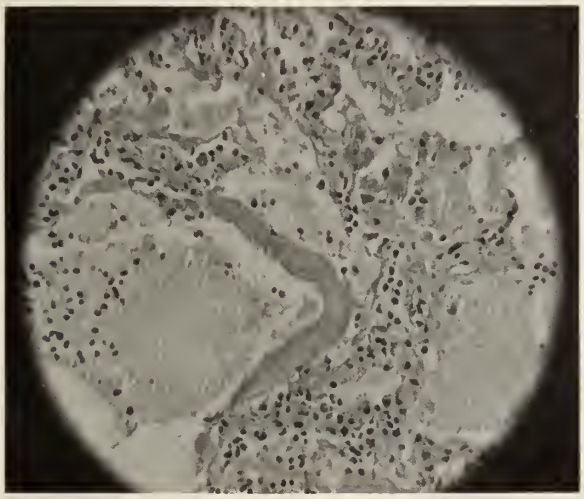

Figure 4.—Microscopic section showing hyaline membrane, (in center of field) edema fluid and polymorphonuclear leukocytes. (H & E stain, reduced from ×200)

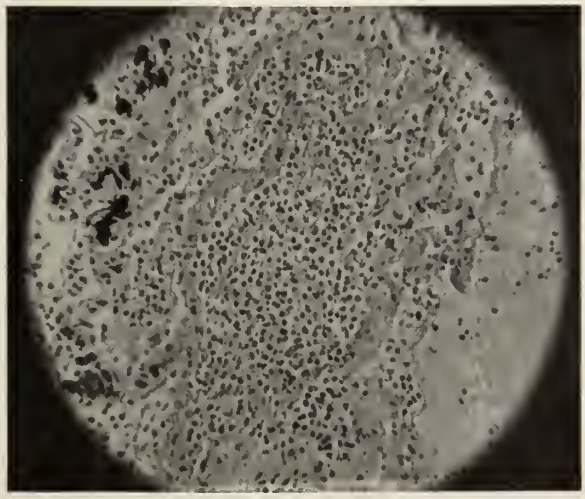

Figure 5.—Microscopic section showing pronounced polymorphonuclear leukocyte infiltration. (H & E stain, reduced from ×200)

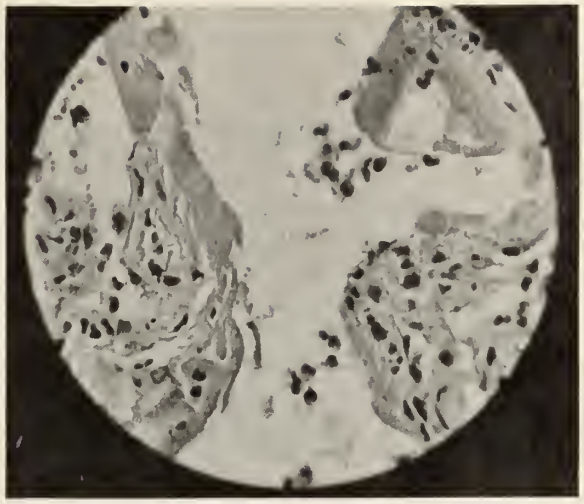

Figure 6.—Microscopic section showing prominent hyaline membranes. (H & E stain, reduced from ×800)

Because the cause of this rapidly progressive pneumonia remained uncertain, an open lung biopsy study was done on the fifth day. This was less than 24 hours after intubation and exposure to high concentrations of inspired oxygen. Study of the lung biopsy specimen (Figures 4-6) showed pronounced polymorphonuclear (PMN) leukocyte infiltration within the alveoli and alveolar septa. There were eosinophilic hyaline membranes present. Some alveoli contained pink, protein-rich edema fluid. There were no granulomas, nuclear inclusions or vasculitis seen. There was no squamous metaplasia or ulceration of the bronchial mucosa. Gram stain showed no organisms. Because of the possibility of Legionnaires disease, erythromycin, 250 mg every six hours, was added to the antibiotic regimen.

On the evening of the fifth day, the first decline in the patient's alveolar-arterial oxygen gradient occurred. Subsequently, slow steady improvement began. Administration of antibiotics was stopped on the 12th day. On the 15th day PEEP was discontinued. By the 21st day mechanical ventilation was no longer required. On the 24th day he became afebrile for the first time and remained so until discharge. Arterial blood gas studies on room air showed a pH of 7.43, a P_{CO_2} of 34 mm of mercury and a P_{O_2} of 70 mm of mercury. The hemoglobin was 11.4 grams per dl; hematocrit, 32 percent; leukocyte count, 11,700 with 69 segmented neutrophils and 6 bands. The sodium value was 135 mEq per liter. Improvement continued to be seen on x-ray studies and

there remained only mild streaking at the left base. He was discharged after 30 days in hospital.

After Discharge

A week following discharge of the patient the Center for Disease Control confirmed the diagnosis of Legionnaires disease. By means of an indirect fluorescent antibody technique the patient's serum was tested against two isolates of the Legionnaires bacterium. The serum taken during the acute phase showed titers of less than 32. The serum taken during convalescence showed a titer of 128 to one of the isolates and showed a titer of 256 to the other isolate. These titers are diagnostic of recent infection with the Legionnaires bacterium. Other serologic studies, including those for plague, tularemia, mycoplasma, Q fever, toxoplasmosis, psittacosis, cytomegalovirus, influenza and adenovirus, were negative.

After the patient had been home for one week, elevations in body temperature occurred to nearly 39°C (101° to 102°F). There was no cough, sputum production, dysuria or diarrhea. The fevers persisted and a 14-day course of erythromycin was instituted. After four days of therapy with erythromycin, the patient's body temperature returned to normal and remained so subsequently. Pulmonary function testing showed that spirometry and lung volumes were within normal range. The patient's condition has continued to improve and he is doing quite well approximately one month after his discharge.

Comment

Legionnaires disease is the name that has been applied to the acute illness that afflicted some 180 people who attended an American Legion convention in Philadelphia in 1976. The cause of the disease was not initially apparent. After much investigative work the etiologic agent was found.[1-3] The reasons for difficulty in discovering the agent were (1) the organism is difficult to culture on standard bacteriologic media and (2) the organism does not stain in tissue sections with usual stains.

Lung tissue obtained postmortem from several patients was inoculated into guinea pigs. These animals became ill and were killed. Portions of spleen, liver and lungs were inoculated into embryonated hens' eggs. The eggs died, and smears of the yolk sac stained by the Gimenez method showed bacilli. Gram stain showed the organism to be a Gram negative rod. The acute and convalescent sera from patients with Legionnaires disease were incubated with this organism, and by means of an indirect fluorescent antibody technique significant rises in titers were shown.

The bacterium is slow growing and difficult to culture. It has been isolated on bacteriologic medium in rare instances from lung tissue and pleural fluid. It has not been isolated from sputum, transtracheal aspiration or bronchial washings. The Center for Disease Control recommends that attempts to grow the organism should be done with Mueller-Hinton agar with hemoglobin and Isovitalex®. In tissue sections the organism stains poorly with Gram stain and Giemsa stain. It does not stain at all with hematoxylin and eosin, acid fast or methenamine silver. The organism can be shown to be present in tissue by means of the dieterle silver impregnation procedure. Most cases are diagnosed by serologic means using an indirect fluorescent antibody technique.

With the advent of this test, it is evident Legionnaires disease is neither localized nor new. The same bacterium caused outbreaks of pneumonia in Washington, DC, in 1965; Pontiac, Michigan, in 1968, and Philadelphia in 1974. Since August 1976 more than 20 sporadic cases have been identified from 11 states. Our case is the first to be documented in the San Francisco Bay area and the fifth in California. The patient did not leave the Bay area in the several months before his illness and undoubtedly contracted the disease here.

In the typical case seen in the Philadelphia outbreak, the earliest symptoms were malaise, myalgia and headache. These were associated with fever which was usually quite high—38.8° to 40.5°C (102 to 105°F)—and a nonproductive cough. Gastrointestinal complaints developed in many patients. When first examined, most patients had rales but no evidence of consolidation. The remainder of the physical examination usually gave normal findings. Leukocytosis with left shift and proteinuria were frequently seen. Less commonly, hyponatremia, mild azotemia, elevated serum glutamic oxalacetic transaminase, or elevated alkaline phosphatase were present. X-ray studies of the chest showed patchy interstitial infiltrates or areas of consolidation which tended to progress. In more seriously afflicted persons the clinical condition usually deteriorated over the next two to three days following hospital

admission. Death from shock or respiratory failure resulted in a mortality rate of approximately 15 percent. Gastrointestinal bleeding was not uncommon. In several patients, acute renal failure was seen. There were no secondary cases noted among either family members or medical staff who cared for the patients. The exact mode of transmission of the disease is uncertain. It is probably acquired by inhalation. It would appear doubtful that it is transmitted from person to person.

Our patient was ill for three days before being admitted to hospital. Surprisingly, he had no respiratory complaints. There was no cough, sputum production or chest pain on admission even though an x-ray film showed right upper lobe pneumonia. Once the patient was admitted to hospital, there was frighteningly rapid progression of the pneumonia. By the fourth hospital day, both lung fields were completely opacified and assisted ventilation was required. The difficulty with oxygenation was severe. At the nadir, the arterial Po_2 was only 55 mm of mercury on inspired oxygen concentration of 100 percent and PEEP of 15 cm of water. This difficulty cannot be ascribed to fluid overload as wedge pressure never exceeded 10 mm of mercury, nor to decreased oncotic pressure as serum albumin remained in normal range. The patient was treated with standard measures for adult respiratory distress syndrome.[4,5] His response was slow but gradual. He remained on PEEP for ten days and assisted ventilation was required for 16 days.

An open lung biopsy study was done less than 24 hours after he was placed on a ventilator and exposed to high oxygen concentrations. The biopsy specimen was characterized by pronounced infiltration with polymorphonuclear leukocytes and the changes consistent with acute alveolar injury. There was a great amount of protein-rich edema fluid and evidence of hyaline membranes. Areas of intra-alveolar hemorrhage were seen. It usually takes several days of exposure to high oxygen concentrations for hyaline membranes and other changes of acute alveolar injury to develop.[6] Their presence on the biopsy specimen obtained so soon after intubation and exposure to high oxygen concentrations would suggest that the major factor producing the pattern of acute alveolar injury was the Legionnaires bacterium.

In a patient with pneumonia in whom no bacterial pathogens have been cultured, the presence of pronounced polymorphonuclear leukocyte infiltration on a lung biopsy specimen should raise strong suspicion of Legionnaires disease. At present, the dieterle silver stain which shows the presence of the organism is not widely available.

TABLE 1.—*Pulmonary Function Test Results*

	Predicted	*1972*	*1977*
Forced vital capacity (liters)	4.6	5.0	4.7
Forced expiratory volume in one second (liters)	3.5	3.9	3.9
Maximum midexpiratory flow (liters per second)	4.7	3.9	4.1
Total lung capacity (liters)	7.0	7.4	6.7
Residual volume (liters)	2.4	2.4	2.1

There have been no randomized trials of antibiotic efficacy in humans. *In vitro* studies have suggested that the organism is sensitive to a number of antibiotics including erythromycin, a number of the penicillins, cephalosporins, the aminoglycosides and chloramphenicol. Erythromycin has been effective against experimental infections in guinea pigs. A case report from the Mayo Clinic suggested that tetracycline was effective.[7]

In our case no statement can be made regarding the relative efficacy of the antibiotics received: methicillin, gentamycin and erythromycin. There was no great change in the clinical course following the institution of any of these agents. The patient remained febrile for more than three weeks and the fever subsided 12 days after all antibiotics had been stopped. Because a definitive diagnosis was lacking while the patient was in hospital, he may not have received optimum antibiotic therapy. The recurrence of fever after discharge suggests that relapse or incomplete irradication of the organism may occur. This fever responded to the reinstitution of erythromycin therapy. One might speculate that patients who are severely ill from Legionnaires disease may require several weeks of treatment with erythromycin or other antibiotics to prevent such recurrences and to hasten recovery.

Several recent papers have reported the pulmonary function status in patients who survived adult respiratory distress syndrome from diverse causes.[8,9] They found no evidence of significant impairment of function. The pulmonary function status of our patient has not changed significantly from that of five years ago (Table 1). An x-ray film of the chest has shown complete clearing (Figure 7). Therefore, Legionnaires disease caus-

Figure 7.—X-ray film of the chest taken ten days after discharge showing complete clearing of the infiltrate.

ing acute respiratory failure does not appear to result in significant permanent pulmonary damage if the patient survives.

The characteristic features of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) include (1) hyponatremia associated with hypoosmolality of serum, (2) urine which is not maximally dilute in face of serum hypoosmolality, (3) continued urinary excretion of sodium despite hypoatremia, (4) normal renal and adrenal function, (5) absence of hypotension, dehydration or azotemia, (6) absence of edema and (7) correction following fluid restriction. On admission to hospital our patient fulfilled these criteria.

There have been several isolated reports of SIADH occurring with bacterial and viral pneumonia.[10,13] The frequency is uncertain, but it does not appear to be high. Fever is one of the known nonosmotic stimuli for release of antidiuretic hormone. Since Legionnaires disease frequently is accompanied by high fevers, the association of this particular pneumonia with SIADH may be more common.

Summary

An isolated case of Legionnaires disease causing adult respiratory distress syndrome was seen in the San Francisco Bay area. This entity should be considered in differential diagnosis of any severe pneumonia. An open lung biopsy study showed pronounced polymorphonuclear leukocyte infiltration, edema fluid and hyaline membranes. Following discharge of the patient there was recurrence of fever, suggesting that relapse may occur. There does not appear to be any significant permanent pulmonary damage if the patient can survive the acute episode. Finally, Legionnaires disease can be associated with the syndrome of inappropriate secretion of antidiuretic hormone.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

More on 'The 11th Myth' About FDA

To the Editor: I am writing in support of Dr. Ungerleider's letter to the editor, "The 11th Myth," published in the February issue of The Western Journal of Medicine, and also in reaction to Food and Drug Administration (FDA) Commissioner Donald Kennedy's letter of rebuttal in the March issue.

I think the concern that Dr. Ungerleider reflects is shared by hundreds if not thousands of physicians across the United States relative specifically to the FDA and, more broadly, to other regulatory governmental agencies. Verification of this hypothesis comes in part from the rapid response we have received from hundreds of the top doctors in the United States in response to our Arnold Mandell Defense Fund. Our nation's top physicians in alcohol, drug and psychiatric care share a common concern with the government's apparent rejection of the concept of clinical judgment and its excessive reliance on the *Physicians' Desk Reference* (PDR) to establish appropriate medical indications and dosage. In this regard, I am also concerned by communications I have received, as a member of the American Medical Association's Drug Abuse Advisory Committee, from the FDA via Dr. Kennedy's office, which indicate they are aware of no alternative regulatory mechanisms to deal with issues such as amphetamine control except through reduction of medical indications. In fact, abundant testimony and documentation have been presented that clearly demonstrate that the vast majority of practicing physicians prescribe responsibly and will respond best to education, consultation and peer communication. Most doctors had decreased or eliminated their prescribing of amphetamines well before the FDA hearings, held to restrict the medical indications for amphetamines in December 1977.

In addition, abundant evidence has been presented that the vast majority of drug diversion via the physician route is coming from a few "script" doctors. The diversion investigation units (DIU) created by the Drug Enforcement Administration (DEA) have been the most appropriate way to deal with these script doctors. For example, I have consulted on two cases recently in which nine script doctors in the city of San Francisco prescribed over 55 percent of the city's Schedule II drugs and two other doctors, in the Santa Clara and San Jose areas in California, prescribed 3.5 percent of the *nation's* supply of Ritalin®. The FDA action on reducing indications for amphetamines or other stimulant drugs will have no impact on these script doctors and only concerted action by both the medical community and the DEA can control such diversion. However, the vast majority of responsible physicians should not be penalized because of the illegal and criminal actions of a few.

I also would like to emphasize some information in rebuttal to Commissioner Kennedy's letter, and as underpinning for Dr. Ungerleider's concern. For example, the Commissioner stated that Canada has eliminated obesity as an indication for amphetamine, apparently to justify support for his belief that equivalent regulatory measures will reduce amphetamine abuse in the United States. In fact, on a recent visit of mine to the Royal Canadian Mounted Police in Toronto, Ontario, they indicated that there has been no diminution in amphetamine abuse since obesity was eliminated as an indication. They further indicated to me that diversion from legitimate practicing physicians was *never* a major source of abuse of these drugs on the street.

I do hope that Dr. Kennedy is sincere in his statement that the "FDA's hopes for communication with health professionals are genuine," for if he is sincere in his desire he will begin to listen to ideas for alternative regulatory mechanisms, vis-a-vis controlled substances and the related concerns of practicing physicians and he will begin to act

accordingly. This would be a major step toward helping reduce some of those very valid concerns expressed in Dr. Ungerleider's letter and showing physicians in general that the "Ten Medical Myths About FDA"[1] really are only myths.

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* * *

TO THE EDITOR: It is difficult not to be saddened by Federal Drug Administration (FDA) Commissioner Kennedy's comments (Correspondence, March issue) regarding Dr. Arnold Mandell, especially at a time when his authoritative voice is so badly needed. In his reply to Dr. Ungerleider's letter "FDA—The 11th Myth" (Correspondence, February issue), Dr. Kennedy states: "As to the bizarre events surrounding Dr. Arnold Mandell's brief involvement with the National Football League, they are obviously beyond the point here—which is perhaps fortunate, since they are also beyond my comprehension." Kennedy quotes his earlier statement (Ten medical myths about FDA, West J Med 127:529-534, Dec. 1977) that " 'the important consideration is whether departure from approved indications is documented by a *legitimate scientific rationale* for such use' (italics added)." He adds "That determination is in the hands of 50 legal jurisdictions, and out of FDA's."

It may be technically correct that FDA has no control over the interpretations placed upon its regulations by the several state boards and agencies. But what the commissioner says about these regulations is very important. The phrase "legitimate scientific rationale" is one that requires some explication. In the case of Dr. Mandell, for example, what would the commissioner accept as "scientific"? Is it scientific to extrapolate from the accumulated experience of physicians who work in the field of drug dependence? Such physicians recognize that one may at times prescribe the very drugs upon which the patient has become dependent, while simultaneously engaging him in a contract to work toward elimination of the dependency. Is this scientific? Is it "legitimately" (if such a distinction is necessary) scientific? One senses, from what Dr. Kennedy does not say, that he views Dr. Mandell's prescribing practices in regard to the San Diego Chargers as failing to meet one (and thus both) of these criteria. If so, it would be helpful for him to say so, making it possible to debate the issues more openly. His comment that the events surrounding the Mandell case are beyond his comprehension is unfortunate, since these events raise issues of vital concern to all physicians. Primary among them is the validity of clinical judgment, *endorsed by fellow professionals who specialize in the same field,* as a guide to therapy. If such judgment does not constitute a "legitimate scientific rationale" then a crisis is in store for American medicine.

The Mandell case also speaks to another issue, not commented upon by Dr. Kennedy: the need to do something about amphetamine self-medication in professional sports. If the FDA is truly concerned about the adverse consequences of improper drug use, it will gird up its loins and take on this long-standing, shamefully neglected, problem. Even if it has no jurisdiction in this area, an official FDA statement confirming the existence of the problem and urging the football establishment to "clean up its act" would be a courageous and effective beginning. Admittedly there are serious political risks in tampering with an industry whose gate receipts and TV sponsorships might be badly hurt by such an intrusion, but Commissioner Kennedy could at least be assured that in this battle he would undoubtedly have the overwhelming support of the medical profession.

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Gerontology and Geriatrics

TO THE EDITOR: In reference to your editorial "Thoughts About Geriatrics" and Alex Comfort's article "Geriatrics—The Missing Discipline?", both contained in the March 1978 issue—A resounding and exuberant bravo.

While the field of gerontology continues to mature at a very rapid pace and impetus has increased in recent times about the issues of human aging and the specialized medical needs of aging and aged persons; data, action and follow-up remain for the most part negligible. There are few gerontologists, researchers and even fewer medical schools and medical practitioners engaged in the training and delivery of medical care to the nation's growing aged population. Historically, the few who have engaged in such research, training and medicine confine their efforts to pharmacological research and inter-

mittent, sometimes questionable medical care in nursing homes, homes for the aged and other like facilities. It has only been recently, as Comfort points out, and largely because of the influx of great numbers of geriatric patients, that the Veterans Administration has gotten involved in geriatric training and geriatric medicine. Here too, however, only a few pockets of such programs exist. Nationwide involvement is bogged down in the quagmire of government bureaucracy. Optimist that I am, however, "a bird in the hand, is worth two in the bush."

A prime reason for our relative lack of medical and scientific concern may well be the dearth of researchers, insightful medical school administrators and medical school students who are trained, want to be trained or even interested, for that matter, in the scientific study of all aspects—medical, clinical and biological—of geriatrics and gerontology. Certainly, we know the financial incentive is just not there.

The American Medical Association and medical schools across this country have a gleaming opportunity in the very palms of their hands—use it! Use that powerful lobby to bring forth needed funds for the development and implementation of geriatric medicine and gerontology training in our medical schools.

It is my deepest hope that the AMA, medical schools and continuing education programs for those in practice utilize the highly trained and skilled gerontologists in the development and implementation of programs dealing with geriatric medicine. Finally, in the allocation of research funds and grants priority should be given to those schools and programs that have geriatric health care and geriatric medicine, developed by qualified gerontologists, included in their curriculum and research projects.

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Thoracic Outlet Syndrome

To the Editor: The article "Thoracic Outlet Syndrome" by Ward W. Woods, MD in the January 1978 issue deserves several comments.

First, I agree, and it is generally recognized, that thoracic outlet syndrome (TOS) may follow a cervical soft tissue injury.

Second, the mechanism involves the initial injury to the anterior cervical muscles with attendant edema and spasm and then shortening and fibrosis of those muscles. The brachial plexus and subclavian vessels are irritated and compressed in the interscalene triangle and costoclavicular space. Prolonged immobilization, that is, greater than 2 to 3 weeks in a cervical collar, in a mild to moderate cervical soft tissue injury is a major contributing factor to the development of TOS. Early treatment includes appropriate use of a cervical collar, physical modalities, muscle strengthening exercises, gentle range of motion exercises, relief of myofascial trigger zones[1] and the use of a unique pillow that provides not only proper head, neck and shoulder girdle alignment but also gentle stretch (when desired) of the anterior cervical muscles.[2] These measures should prevent the syndrome from developing except in a very small percentage of patients. Therefore, a 23 percent incidence is somewhat tragic. Dr. Woods points out an average of a 14-month time lapse between the original injury and his first examination. Obviously, Dr. Woods is not involved in the early care of these patients and is not responsible for the apparent physical mismanagement of these soft tissue cervical injuries.

Third, Dr. Woods reaches the diagnosis of TOS on the basis of 20 signs and symptoms and acknowledges that some of the 20 are due to a vertebrobasilar artery syndrome. I was not aware that vertebrobasilar artery symptoms and signs could be considered to be part of the TOS and, therefore, Dr. Woods' apparently high incidence of 23 percent might be explained not only by early mismanagement but, also, by a unique expansion of the usual diagnostic criteria of TOS. Furthermore, some of the 20 signs and symptoms could be explained by myofascial trigger areas in the sternomastoid muscle[3] (postural dizziness and blurred vision), trapezius muscle[3] (retro-orbital pain), scaleni[4] (anterior and posterior chest pain). Discharges from trigger areas may also be accompanied by vasoconstriction and other autonomic effects in the reference zone of pain.

Fourth, Dr. Woods' preoperative treatment in the 459 TOS cases may have been too little and too late, especially if treatment of myofascial trigger zones and cervical joint mobilization techniques were not utilized.

The fifth and final point relates to Dr. Woods' operative procedure of transection of the anterior

scalene muscle and periarterial stripping and lysis of the brachial plexus. Dr. Woods indicates that excision of the first rib is rarely necessary. The surgical treatment of TOS seems to keep changing. In the past, scalenotomy was replaced by first rib resection. Roeder and co-workers[5] indicated that "based upon the work of many authors, it is now apparent that first rib resection is the preferable mode of operative decompression of the thoracic outlet" and "the first rib is the common denominator to all forms of thoracic outlet compression." More recently, there is a trend back to scalenotomy for TOS. One wonders if the choice of procedure should, perhaps, depend on the cause of the TOS.

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Outpatient Self-Administration of Parenteral Antibiotics

To the Editor: Dr. Antoniskis' timely report (Antoniskis A, Anderson BC, Van Volkinburg EJ, et al: Feasibility of outpatient self-administration of parenteral antibiotics. West J Med 128: 203-206, Mar 1978) about the feasibility of outpatient self-administration of parenteral antibiotics emphasized a safe and effective modality of treatment helpful to slow the rapid rise of health care expenditures. I hope that reviews such as this will be funded generously, to supply further proof that some procedures can be performed safely outside the expensive (hospital) setting.

TABLE 1.—*Several Intravascular Procedures That Have Been Done in Patients' Homes*

Intravascular Procedures	*Hospital*		*Physician's Office*	*Patient's Home*		
				Trained		
	Inpatient	*Outpatient*		*Nurse*	*Helper*	*Patient*
Antibiotics	+	+	+			
Blood	+	+	+			
Chemotherapy	+	+	+			
Arteriovenous access						
Antibiotics	+	+	+	+	+	+
Blood	+	+	+	+	+	+
Deferoxamine	+	+			+	+
Hemodialysis	+	+	−	+	+	+
Hyperalimentation	+	+	−	+	+	+
Iron	+	+		+	+	+

Table 1 lists several intravascular procedures that have been done in patients' homes. Some, such as the administration of blood, have run into considerable opposition, motivated by the fear of legal problems. Others, such as dialysis at home, have shifted to outpatient "limited care" clinics, although patients dialyzing at home fare better, with a higher degree of rehabilitation and employment, at a considerably lower cost.

The question arises whether an insurance carrier must pay for the hospital admission of a patient for procedures that can be safely done on an outpatient basis or in a patient's home. Several carriers insist that the last hemodialysis before the kidney recovers enough function to not require further treatment (in the treatment of acute renal failure) be done while the patient is confined in the hospital, even though some stable patients can be cared for in their homes between dialyses and could receive dialyses on an outpatient basis.

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Refer to: Nelsen AC: A medical resident in Ponape (Medical Education). West J Med 128:453-458, May 1978

A Medical Resident in Ponape

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The University of Hawaii has an elective two-month primary care rotation in Ponape, in the Eastern Caroline Islands, for senior medical residents. Many diagnostic and therapeutic situations provide unusual challenges because of the tropical environment and the paucity of medical facilities. Parasitoses, tuberculosis and trauma are common, and certain diseases, such as cholelithiasis and coronary artery disease, have a low incidence, reflecting the socioeconomic conditions. The local intoxicant, sakau, seems to be responsible for dermatologic, pulmonary, and possibly hepatic and neurologic disorders.

The rotation has proved to be a worthwhile educational experience for residents and a benefit to the people of Ponape.

PONAPE is a district in the Eastern Caroline region of the Trust Territory of the Pacific Islands, an American protectorate since the end of World War II. The main island, Ponape, is covered by a 130-square-mile mountainous tropical rain forest. It is located at 7° north latitude, 158° east longitude, approximately 3,200 miles from Honolulu. Other islands in the district include numerous atolls to the east and south, some of which are uninhabited and some with populations ranging up to several hundred people.

As senior medical resident in the University of Hawaii Integrated Medical Residency, I worked in Ponape during a two-month elective rotation. I functioned as the primary physician and consulting internist for this island population of nearly 20,000, and was responsible for the 30-bed medical ward, as well as for inpatient and outpatient consultations.

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The practice of medicine in Ponape presents many unique and fascinating aspects. Problems are those common to most underdeveloped areas —for example, deficiencies in sanitation, nutrition, communications and transportation. The situation promises to improve with the planned opening of a $6½ million referral hospital in the main town of Kolonia. Changes will be slow because the population will need time to adjust. New facilities, including a modern laboratory, surgical suite and hemodialysis unit, will be available. However, major training programs for paramedical personnel and improvements in delivery of medications and equipment (including repairs) will be necessary to utilize the hospital properly. The new hospital administrator for the Trust Territory is capable, hard working and realistic in his approach to modernizing health care delivery.

At present there is no real teaching for residents in Ponape except through visiting professors

from Honolulu. Once established, the new hospital will have American-trained specialists, subspecialists, and heads of ancillary and paramedical facilities. The inability of physicians to obtain continuing medical education credits may be overcome if and when satellite communications are established for this purpose. Until then, however, the rotation should be limited to senior residents because of minimal supervision. Also, two months clearly is a minimum period to fully appreciate and learn from the experience; this length of service should be maintained. This may also permit residents to upgrade care in peripheral clinics previously deprived of visits by a physician.

Medications are limited in number and supply. Equipment is often in disrepair, awaiting parts for many months. Before leaving Ponapc, I submitted a list of medications and less expensive instruments I believed would be useful. A major problem is correcting shortages before they become critical.

The Patient Population

The population of Ponape is heterogeneous. In addition to those native to Ponape, a large number of Micronesians from atolls, islands and other districts live there—each group with its own culture, attitudes and even particular tendencies to certain illnesses. Dealing with the patient population requires a basic knowledge of the language, which I was able to acquire without much difficulty. Although most people converse in Ponapean (there are no dialects, only varied accents), and some speak English, a fair number know only their own outer-island speech. Occasionally, no one at the entire hospital will speak the language of a particular patient, which may be Mortlockese, Pinglapese, Nukuoran, Trukese, Palauan or another rare native tongue. Translation is often laborious, particularly so because patients tend to be taciturn about their problems. "Eye talk" is often a replacement for the spoken word, and even subtle facial expressions may have an important meaning. Common, high, royal or high royal vocabulary is used, depending on whom one is addressing. Understanding the language and culture is difficult for an outsider, but it is appreciated by patients and helps to gain their confidence.

Taking a history is always tedious and absolutely no questions must be omitted, even the most obvious, because patients will not volunteer information even when asked about a closely-related symptom. Few medical records have been kept, old charts are not much help and Ponapeans generally know little about their medical history. Certainly, drug names are inconsequential to them. Efforts to teach patients about their ills, proper instructions on the importance of adequate treatment and follow-up, and especially education about prevention often seem to fall on deaf ears but must be continued. I gave some instruction on basic problem-oriented charts, and health personnel need to have record keeping stressed.

Many recommendations or treatments we take for granted in Hawaii are difficult in Ponape. The people generally have no means of refrigerating medicines. Their diet is quite limited, making further restrictions unreasonable or impossible. Diabetes mellitus, therefore, is particularly hard to manage. Even such time-established public health measures as boiling all drinking water are difficult for many people.

Discharging a patient is an event worthy of much thought. Almost without exception the usual custom elsewhere of asking a patient if he or she would like to go home is met with a quizzical or amused look. Discharge is exclusively the physician's decision. The tendency to "follow up problems as an outpatient" is not always easy. A patient who does not feel completely well before discharge may seek local cures, or he may live far from town—even on an atoll 500 miles away—making returns to the clinic difficult. The few roads are paved with coral, and are in constant disrepair.

In general, the population is naive about its health, which makes firm direction by an open-minded physician imperative.

Local Medicine

It is a struggle to learn about native medicine, or winni. There are certain people who are known to be healers; they have well-guarded secrets, retaught in a closed system and shared reluctantly. Local dictum states that he who tells all he knows will surely die. Nonetheless, I found that native medicine is of four basic types: massage, spells, lotions and scents, and internally taken preparations.

There is often competition between local and occidental therapy. The two should not be mixed, despite patient requests, or confusion will reign. Some home remedies may indeed be effective, but no studies have been done to determine which are valid. A patient may be ill or he may

be "Ponape sick," against which malady Western medicine may not be effective.

The secrecy and lack of objectivity involved are overt and lead to claims of cures without justification. Research into these areas might prove worthwhile.

Daily Routine

The present hospital facility in Kolonia, Ponape, is old and in disrepair. It consists of an outpatient building, gynecological-surgical, obstetrical-pediatric and medical wards. The latter includes 28 beds which are easily kept full. The outpatient load is variable; I saw about 10 to 12 clinic patients a day at the end of my rotation. These were either discharge follow-ups or referrals from Medex (physicians' assistants), from the Fiji-trained medical officers, or from other towns or islands. Americans who fell ill, or tourists, were generally referred to me or came directly.

Facilities were at a minimum. Laboratory work consisted of complete blood counts, analysis of urine, blood glucose studies, cultures and tests of stool specimens for ova and parasites. X-ray equipment was available, and I often did my own fluoroscopy. An electrocardiograph was in working order, and I improvised a Master exercise test for angina pectoris. A proctosigmoidoscope was available, but no cystoscopy or gastroscopy could be done during my rotation.

Late evening or night rounds to check on new admissions or problems, and to make sure orders were being carried out properly, were a necessity. Emergencies often required that the ambulance driver seek out staff members—such as the surgical team or me—at various points in the community because few people had phones. I was on backup call every night and was often called in when difficult problems arose.

While in Ponape, I began a series of visits by boat to distant villages and dispensaries around the island. Some of these had never been visited by a physician. Local health assistants were contacted by radio in advance and were requested to present their problem patients on those occasions. Some of these patients required transfer back to the district hospital for further workup. Therefore, the hospital in Kolonia, although primitive, served as a referral center. This was also the case when patients were transferred from other islands.

Seriously ill patients could not always be sent to Guam or to Honolulu because of limited funds available for that purpose, and a strict screening procedure was used. I was one of three members on the screening committee. Critical patients who would not survive transfer occasionally required near-heroic measures, at which times the staff generally responded very well. I taught cardiopulmonary resuscitation, and emergency resuscitation was carried out on several occasions when there was hope that a patient could survive without sophisticated life-support systems.

Common Diseases and Etiologic Considerations

Dermatology

The traditional local intoxicant in Ponape is sakau, made from the root of the sakau plant (Piper methysticum). It is similar to kava. In small doses it has a local anesthetic effect on the oropharynx. Higher doses cause a generalized numb feeling, depressed sensorium and decreased psychomotor activity. It may be implicated in dermatologic, pulmonary, gastric and neurological pathology. I have not discerned a tendency toward fatty infiltration or cirrhosis of the liver, although this had been conjectured by others. One 45-year-old Ponapean man who drank sakau heavily for many years was admitted to Ponape District Hospital for control of rapidly progressive guttate psoriasis. In addition to the generalized psoriasiform rash, he had severely dry skin, in places almost parchment-like. Treatment consisted of what was available: coal tar, triamcinolone acetonide cream (Kenalog®), sedation, sun exposure, vitamins and abstinence from sakau. The condition improved over five days and the man was discharged, only to suffer a flare-up requiring transfer to Honolulu for chemotherapy with methotrexate. That this was related to renewed sakau intake is a serious question in my mind.

Missionaries who drink sakau have found that skin dryness decreases if multivitamins are taken, substantiating earlier Japanese reports that there may be a sakau-induced avitaminosis.

Tinea versicolor is epidemic; I would estimate that nearly three quarters of the population are affected. Treatment is infrequently sought. Other skin infections are common: impetigo, molluscum contagiosum (often with secondary bacterial infection) and furunculosis. Cellulitis is common,

related to frequent minor trauma to the lower extremities. Poor hygiene is undoubtedly a factor. Luckily, nearly all Staphylococcus aureus is sensitive to penicillin.

Leprosy is still prominent in Micronesia. Pinglap is long known as an area affected, and previously served as a pilot project for studying the effects of long-term DDS (dapsone) therapy in reducing the incidence of leprosy in a large population.

As in many other areas of the Pacific, a positive Venereal Disease Research Laboratories test is usually indicative of previous yaws when found in an older person, but usually indicates syphilis in a younger person. In Ponape, an increasing number of positive serologies have been noted in prenatal screening being conducted by Dr. Richard Guidotti, Bologna Medical School. Follow-up is being done at present.

Finally, I treated one woman for probable fulminant meningococcemia. She died as her young son had died several months before, which prompted me to recommend treatment of the remaining family members with penicillin.

Pulmonary

Pulmonary disease is one of the more common problems in Ponape. Asthma appears to occur more frequently than in Hawaii, accounting for roughly 5 percent of admissions. In outpatients, asthma often is not responsive to the limited medications available. Many people feel that sakau drinkers have a high incidence of asthma, but the causes for transient small airway obstruction appear to be multiple. During the dry season, coral dust seems to play a role in bronchospasm, as well as inducing a vasomotor rhinitis. An allergic component may be significant (for example, coral dust and fungus), but the frequent coexistence of intestinal parasitosis makes eosinophilia hard to interpret. This also causes speculation as to a pathogenetic role of parasitic larval migration through the lung inducing bronchospasm (Loeffler syndrome). Severe gastritis-duodenitis from heavy helminthic infestation triggering an asthmatic attack is a common clinical finding.

Tuberculosis is still endemic in Ponape. The reported incidence has been about four new cases per month, but this is certainly a conservative estimate. For half of my rotation, no purified protein derivative (PPD) or tuberculosis culture medium was available. I did care for patients with positive PPD tests, patients with pulmonary tuberculosis, presumed or proven vertebral or peripheral tuberculous arthritis. One outpatient had just recovered from tuberculous meningitis, treated by another medical resident. The frequent coexistence of asthma and tuberculosis makes the use of steroids for the former condition hazardous, although sometimes necessary.

Chronic obstructive pulmonary disease, pyogenic lobar pneumonia, posttraumatic empyema (one patient with a gastropleural fistula) are also common. One patient probably had pulmonary embolus, and another was a diabetic with diffuse interstitial pneumonitis (possibly streptococcal) who recovered after a prolonged hospital course.

Cardiovascular

One of the more common cardiac disorders encountered in Ponape is rheumatic heart disease. This accounts for a large number of referrals to Hawaii, both for valve replacement and for endocarditis. I cared for patients with all stages of the disease, from new acute rheumatic fever to end-stage congestive heart failure with ascites secondary to valve disease. Problems are numerous. Rheumatic fever prophylaxis is generally carried out well by the local public health service. However, little consideration is given to endocarditis prophylaxis despite the generally poor dental hygiene of the population. Three patients had suspected subacute bacterial endocarditis. One died during therapy, one was transferred back to Honolulu for dialysis—renal failure probably due to endocarditis-induced glomerulonephritis—and the third was discharged well. Patients with prosthetic valves cannot be fully anticoagulated because of inadequate laboratory facilities.

Coronary artery disease is not as infrequent as I was led to believe. In two months, there were five acute infarctions and one or two people each week were seen for angina pectoris. One myocardial infarction was in a Caucasian. As Western civilization encroaches upon the islands, coronary atherosclerosis seems to accompany it. Most of these patients were either politicians or agency directors.

A high blood pressure detection program has just been started, and early statistics suggest about a 7 percent to 10 percent incidence among the general population.

Cardiomyopathy may be a diagnosis of exclusion, but with available facilities, I felt three pa-

tients were admitted to hospital with this clinical entity in the two months I was in Ponape.

Infectious Disease

Pathogenic organisms of many kinds seem to flourish in this tropical environment. Gastrointestinal parasites are a major cause of hospital admissions and of outpatient visits. The most common pathogens causing upper gastrointestinal symptoms are ascaris and hookworm, the latter sometimes simulating pancreatitis. Strongyloides stercoralis is not uncommon. Bloody diarrhea with tenesmus is amebic in origin until proven otherwise, and cyst carriers are very common. There seems to be sensitivity to the commonly used amebicides. Viral hepatitis is four times more common than in the United States, but the question of amebic hepatitis often enters into the differential diagnosis. Poor personal hygiene and polluted water around the town of Kolonia affecting local mollusks probably play a role. The children around the hospital had a habit of playing with used needles and syringes. However, we took measures to halt this: special needle disposal procedures, education of hospital employees and education of the general population. The island of Truk has a high incidence (about 10 percent) of children with positive hepatitis B surface antigen (HB_s Ag), but the incidence in Ponape is probably as high.

I also introduced the concept of infectious disease control in the hospital itself, emphasizing frequent hand-washing and employee health standards with periodic PPD tests and stool specimen examinations.

Routine follow-up studies for ova and parasites in stool specimens were begun for discharged, treated patients.

Rheumatologic Disorders

I encountered a surprisingly high incidence of arthritis in Ponape. Septic and crystal-induced arthritides were common. Inflammatory joint disease of various types was encountered: rheumatoid arthritis, ankylosing spondylitis, pancarticular juvenile rheumatoid arthritis and acute rheumatic fever.

Miscellaneous

Although I encountered no cases of poisoning while in Ponape, siguatera intoxication is known there, mostly from larger carnivorous fish, such as barracuda. Also, some types of wild tapioca have caused death or severe gastroenteritis when eaten mistakenly.

Suicide is more common among men; the most common method is by hanging. Drug overdose was not a problem, but fairly liberal outpatient use of narcotics occasionally leads to addiction or abuse.

Diving accidents will be a problem of the future because scuba diving has only recently been introduced in Ponape. One case of the bends was encountered before my arrival. There is a small decompression chamber in Saipan and a larger one in Guam. As both local residents and tourists dive, the incidence of stings from rays, cones and stonefish, as well as the number of shark and barracuda attacks, may increase. Fortunately these are now rare.

Without a good study, Ponapean medical officers feel there is a very high incidence of thyroid nodules in Ponape. Two patients with solitary nodules with normal thyroid functions are now awaiting elective resection. Infertility is a serious problem, although infrequent. It carries a great social stigma. Clomiphene citrate may soon be in use.

Although trauma was more the concern of the surgical ward, I came in contact with several interesting cases. Violent acts are not uncommon, especially since weekend drinking of alcohol is almost always excessive. Two patients with cranial trauma requiring emergency craniotomy were cared for during my rotation. One had a subdural, the other an acute epidural hematoma. Both patients did well.

Knifings and spear injuries are common. Car and motorcycle accidents are increasing, and will be a major problem when the roads are paved with asphalt over the next few years.

Occupational hazards exist. Night fishermen are sometimes the victims of a curious form of trauma caused by the hemiramphus quoyi, or halfbeak fish. When these fish are attracted by a light at night, they sometimes inflict injury. Two men were skewered in the thigh, and a third suffered a partial pneumothorax from a halfbeak injury to the chest.

There was no dietitian at the hospital. The kitchen employees had no concept of diet therapy or even of calories. Therefore, any special diet had to enumerate specific foods to be given or avoided, and the quantities to be given. The people eat mainly rice, taro, yams, bananas, co-

conut, fish and some chicken. Canned goods are becoming very popular. Beef is fairly expensive. It is tempting to attribute the near absence of cholelithiasis and the traditional low incidence of coronary artery disease at least in part to the diet, which is high in bulk and low in animal protein and fat. I saw only rare instances of primary malnutrition, and those were in children.

A vigorous cancer detection program by Papanicolaou smears shows a very low incidence of cervical carcinoma. There seems to be a fairly high incidence of molar pregnancy and of choriocarcinoma, however. One woman gave birth to a second child with "colloidon skin."

I witnessed a fascinating neurological abnormality in a 60-year-old Ponapean man in whom overt but fully reversible choreoathetosis developed when he was intoxicated with sakau (sakau la). Until my departure, results of neurological studies in this man were normal when he was not "sakau la."

Academic Value of the Rotation

Although at present there is no formal teaching for residents who elect the Ponape medical rotation, the experience itself is invaluable, and it should improve with the opening of the new district hospital. First, much could be learned from even limited research into pathogenetic mechanisms contributing to Ponapean health problems, and this should be encouraged. This type of experience is mutually beneficial to Ponape and to Hawaii and its university housestaff.

Second, a physician-in-training who finds himself or herself without sophisticated laboratory and diagnostic aids must revert to the basic skills of taking histories and doing physical examinations. Management becomes largely a challenge to clinical acumen. These basics need renewed stress in medical education where the thrust of training is directed toward primary care and adequate health care delivery to rural areas.

A medical resident in Ponape has an enormous responsibility. He is the medical authority for thousands of people with complicated socioeconomic and health problems. Innovation, great energy and adaptability, qualities to be cherished in any physician, are required. Consultation is obtained mainly through costly transfer, and cannot be requested without good reason. Varied problems are encountered, especially when obstetrical and gynecological, surgical, and pediatric consultations are taken into account. This kind of responsibility is good for a medical resident who is about to enter private practice.

Finally, this rotation may allow a resident to witness diseases not otherwise seen. Acute rheumatic fever, amebic dysentery, certain forms of tuberculosis, leprosy, diving accidents and vitamin deficiencies are disorders we read about but seldom have occasion to treat.

Refer to: Rudin E, Zimmerman R: Psychiatric treatment—General implications and lessons from recent court decisions in California (Medical Jurisprudence). West J Med 128: 459-466, May 1978

Psychiatric Treatment

General Implications and Lessons From Recent Court Decisions in California

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The California legislature enacted tight constraints on the use of psychosurgery and electroconvulsive therapy in 1974. In April 1976 a State Court of Appeals declared part of the law to be unconstitutional. In doing so, the court enunciated several principles for regulating medical procedures. It affirmed the inherent police powers which permit the state to safeguard the public, especially incompetent, involuntary or confined persons, with respect to intrusive and hazardous medical procedures and to procedures which affect thought or feeling. Although limited to legislation concerning two psychiatric procedures, the court's decision, and subsequently enacted legislation governing these procedures, has implications for other medical procedures and for other parts of the nation.

In June 1974 California Assemblyman John Vasconcellos (D-San Jose) introduced Assembly Bill 4481 in the California legislature. It amended those sections of the state's Welfare and Institutions Code that defined the rights of mental patients. Among its other provisions it prohibited the use of lobotomy, convulsive therapy or drug therapy without the written consent of the patient. The bill was complete and simple.

The initial proponents, who had brought the matter to Assemblyman Vasconcellos' attention and had elicited his sympathy, were organized into a group known as the Network Against Psychiatric Assault (NAPA). At that time NAPA was a small group of ex-psychiatric patients and a handful of sympathetic other people, including psychologists, psychiatrists and lawyers. The organization was active in the San Francisco Bay area, having already begun to make demands of the Langley-Porter Neuropsychiatric Institute at the University of California, San Francisco.

Soon the California Medical Association, the California Hospital Association, the California Conference of Local Mental Health Directors, and the Association of California Branches of the American Psychiatric Association challenged the bill. After several meetings of the proponents, the opponents, the bill's author, and the legislator's administrative aide; after testimony in two state Assembly and two state Senate committees; and after six amendments, the bill was passed

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by both houses of the legislature with only one dissenting vote.* It was signed by Governor Ronald Reagan on September 27, 1974.

A Brief Summary of AB 4481

As finally enacted, AB 4481[1] provided that each person involuntarily detained for evaluation or treatment, each person admitted as a voluntary patient to a state hospital, a private mental institution, or a county psychiatric hospital, and each mentally retarded person committed to a state hospital would have the right to refuse shock treatment (electroconvulsive therapy) and to refuse psychosurgery. The latter was defined as lobotomy, psychiatric surgical operation and behavioral surgical operation and all other forms of surgical procedures on the brain done specifically for the purpose of modifying or controlling thoughts, feelings, actions or behavior, whether the surgical procedure modified normal brain function or tissue or abnormal brain function or tissue, when the abnormality was not an established cause for those thoughts, feelings, actions or behaviors.

The bill required the treating physician who believed the shock treatment to be medically indicated to explain to the patient *and* a responsible relative or guardian or conservator all of the following:

- The procedures used in carrying out shock treatments.
- The benefits to the patient of the procedure.
- All of the possible risks and side effects.
- The nature and seriousness of the patient's disorder.
- The degree of uncertainty of the benefits and hazards of the procedure.
- Reasonable alternatives therapies.
- The right to revoke consent at any time before or during treatments.
- The conditions under which the treatments might be given without patient consent.

Shock treatment would be done only after the patient had given written informed consent—dated, witnessed and entered in the patient's treatment record, including a statement that the treatment physician had made the required oral statement; that the patient had the capacity to give informed consent; that a responsible relative or the guardian or conservator had been given the required oral statement, and that the treating physician had documented the following in the patient's treatment record:

- The reasons for the procedure.
- That all other appropriate treatment modalities had been exhausted.
- This mode of treatment was critically needed for the patient's welfare.

In addition, review by a committee of three physicians—one appointed by the facility and two appointed by the local mental health director (two of the three physicians Board certified in psychiatry or neurosurgery)—was required. After review of the case and the treatment record, the committee had to agree unanimously with all the conclusions of the treating physicians about the patient and the treatment.

If the treating physician or the review committee determined that the patient was unable to give informed consent, shock treatment would be carried out only after it was established that the review committee unanimously agreed with the treating physician as to the reasons for the procedure, the exhaustion of all other appropriate treatment modalities and the critical need for the treatment, and that a responsible relative or the guardian or conservator had been given the required statement.

No shock treatment would be given to a patient who was able to give informed consent and refused to do so.

No psychosurgery could be carried out without the written informed consent of the patient, or of the parent or guardian of a minor patient. In obtaining the consent of the patient and a responsible relative or guardian or conservator, the treating physician would orally explain the following:

- The procedures used in psychosurgery.
- The benefits to the patient.
- All possible risks.
- The nature and seriousness of the patient's disorder.
- The degree of uncertainty of the benefits and hazards.
- Reasonable alternatives.
- Absolute right to refuse or revoke consent at any time before the surgical operation.

Psychosurgery would be done only after all of the requirements for electroconvulsive therapy (ECT) had been met, including unanimous agree-

*At no time in any of these hearings was testimony presented indicating the numbers of patients receiving electroconvulsive therapy or psychosurgery, the incidence of inappropriate use, or the rate of identified complications. Unethical practice and sexual and economic discrimination were alleged and anecdotal experiences were angrily reported. Professional literature on effects and side effects was quoted by both sides.

ment of a review committee of three physicians and at least a 72-hour delay between the written informed consent and the surgical procedure. A responsible relative was defined as the spouse, parent, adult child, or adult brother or sister of the patient.

Any physician who violated any of these provisions would be subject to a civil penalty of not more than $10,000 per violation or revocation of license, or both. Civil action could be brought for damages, and for judgment, a reasonable attorney's fee, and costs of the action.[2]

Existing law also authorized the state's Director of Health to adopt regulations governing denials of patients' rights, with such denial entered in the patients' treatment records. Each local mental health director was required to report quarterly to the Director of Health the number of persons in each facility whose rights were denied and which rights were denied. The reports were to be in such form as to "enable the Director of Health to identify individual treatment records" for further analysis and investigation. On request, the reports were also to be available to state legislators or county supervisors. Treatment record information pertaining to denial of rights was also to be available to the patient, attorney, conservator, guardian, state Department of Health, state legislators or county supervisors.[3]

Ten major clinical practice issues were identified at the time AB 4481 was enacted:

1. Access to the clinical record of a voluntary patient by a responsible relative and a review committee of three physicians was an invasion of that patient's privacy, a breach of medical confidentiality, and a potential detriment to the patient's welfare.

2. Outpatient ECT (and possibly ECT done on a voluntary patient in a general hospital) was exempted from the legislation.

3. The information required to be given to the patient and the relative was so excessively broad as to invite litigation.

4. The information required to be given allowed no exercise of clinical judgment and, therefore, was contrary to informed consent definitions rendered by the California Supreme Court in *Cobbs vs Grant,* the existing model for informed consent regarding all other medical practice.

5. Differences of professional opinion as to what constituted "exhaustion" of "all" other "appropriate" treatment modalities and "critical need" seriously increased the risk of serious penalties (loss of license and $10,000 fine) and malpractice litigation.

6. The delay of use of ECT until all other modalities had been exhausted, when the procedure might be considered specific for the psychiatric syndrome presented, would increase hospital stays and treatment costs.

7. Mandated consultation, replacing voluntarily obtained peer consultation, was a major breach of peer review and peer regulation mechanisms in widespread use in medicine and a dangerous precedent for all of medicine.

8. The excessive civil penalties and increased risk of malpractice suits would probably deter many physicians from utilizing an important, proven treatment modality in California.

9. Access to the clinical record of any patient who received ECT, by the Department of Health, state legislators and county supervisors, was a breach of medical confidentiality by state and local government.

10. A legislature's proscribing and prescribing clinical procedures, without specifying and negotiating its concerns with the profession involved, was a dangerous precedent, inviting further arbitrary, ill-considered, poorly informed, unilateral decisions affecting the quality of human life and patient care.

The Judicial Process

In December 1974 an injunction was issued by a Superior Court in San Diego. A temporary order restraining implementation of AB 4481 remained in effect pending a decision by the Fourth District Court of Appeal of the State of California. However, there was doubt as to the scope of the restraining order. Many physicians and hospitals in California refused to give the treatments in question. Others attempted to comply with the new law, as each interpreted it.

For over a year this was the uncertain situation regarding the use of ECT and psychosurgery in California. The author of AB 4481 introduced remedial legislation, AB 1032 (in the 1976 session), which underwent its own stormy course further beclouding the scene.

Then, in April 1976, the Court of Appeals rendered a decision, finding certain provisions of AB 4481 unconstitutional.[4] In May 1976 it modified the decision, stating that while it could not separate the constitutional from the unconstitu-

tional portions of AB 4481, it was not invalidating all the portions of the Welfare and Institutions Code pertaining to the rights of patients.[5]

Valid Regulation of Certain Medical Treatment

In a lengthy opinion the court ruled that (1) the requirement that these treatments be ". . . critically needed for the welfare of the patient" was unconstitutionally vague, (2) the requirement of informing a "responsible relative" of the treatment was an unconstitutional invasion of privacy, (3) the application of certain informed consent requirements to competent and voluntary patients seeking ECT was unconstitutional and (4) the failure to provide for an adequate hearing for patients on the issues of competency and voluntariness was a denial of procedural due process. Penalties related to the unconstitutional provisions of AB 4481 were also invalidated. The court ordered a peremptory writ of mandate to issue, preventing the Attorney General, the Director of Health, and the Board of Medical Examiners from enforcing the invalid provisions. The State decided on no further appeals.

The decision is significant not only for its immediate effect as to the permissible scope of regulation of psychosurgery and ECT, but also for the regulation of any medical treatment that could be considered "intrusive and possibly hazardous."

Applying standard constitutional doctrine, the court noted that the public health and safety can be regulated by the legislature and that reasonable classifications of treatment can be established as long as they are not arbitrary and are based on some differences having a substantial relationship to a legitimate legislative purpose. The court also noted that certain requirements for informed consent by mental patients were appropriate as the competence of such patients to consent to treatmentment is questionable when compared with that of other patients. Also, the ability of mental patients to accept treatment voluntarily is questionable and in many instances the label of "voluntary" is an artificial description. The court rejected the contention that requirements that explanations be provided for all possible risks, possible side effects, and the degree of uncertainty of the benefits and hazards associated with the procedure were void for vagueness. The court stated that the statutes merely required a full explanation to the patient of all relevant information.

Here the court was speaking to the ability of a mental patient to consent to any treatment, not just psychosurgery, ECT or the treatment of the mental illness. The court essentially held that for any "intrusive and hazardous procedure" the legislature may impose requirements pertaining to informed consent which go beyond those generally required in California for other modes of treatment by *Cobbs vs Grant*.*

The court further declared that

> Mental patients are distinct from other ill patients in two special circumstances. First, their competence to accede to treatment is more questionable than that of other patients. Mental patients' incompetence may not be presumed solely by their hospitalization (§5331), but it is common knowledge mentally-ill persons are more likely to lack the ability to understand the nature of a medical procedure and appreciate its risks. Second, their ability to voluntarily accept treatment is questionable. The impossibility of an involuntarily detained person voluntarily giving informed consent to these medical procedures is fully treated (elsewhere) . . . Voluntary patients . . . are susceptible to many of the pressures placed on involuntary patients. The Legislature's inclusion of these "voluntary" patients recognizes the fact the "voluntary" label is a creation of the Legislature, and often only means the patient did not formally protest hospitalization. These circumstances make the separate treatment of mental patients clearly rationally related to the objective of insuring their rights to refuse treatment.[4(p674)]

The petitioners argued that the requirements that explanations be provided for (1) all possible risks and side effects and (2) the degree of uncertainty of the benefits and hazards associated with the procedure should be void for vagueness. The court rejected the argument, stating that the statutes merely required a full explanation to the patient of all relevant information. This had been a major deterrent to the administration of these treatments. The "all" requirement suggested a high risk for omission of some rarely found risk or side effect. The court's interpretation still left the decision as to what can be omitted to the individual physician's judgment—pending a retroactive decision in litigation or administrative action.

AB 1032, the "remedial" legislation enacted in 1976 and signed by Governor Brown, no longer requires that "all possible risks and possible side effects" be disclosed. The statute now reads "The nature, degree, duration, and the probability of the side effects and significant risks, commonly known by the medical profession . . ."[6] The court

*Indeed, the Lanterman-Petris-Short Act has since been amended to require specific authorization of all medical procedures for conservatees.

had held that "whatever may be the wisdom of such a strict standard of disclosure," AB 4481's wording was not unconstitutionally vague. This could apply to such all-inclusive wording were it to appear in future legislation.

AB 4481 also required the treating physician to determine that "all other appropriate treatment modalities have been exhausted." Psychiatrists protested that this required an exhaustive use of psychotherapy, medication (sometimes with serious side effects) and therapeutic milieu with a possibly suicidal or otherwise acutely ill patient for whom ECT was the treatment of choice. However, the court interpreted "appropriate modalities" as meaning "any forms of treatment medically appropriate for a *particular* patient with a *particular* condition [court's emphases]. Alternative forms have been 'exhausted' when they have been tried and found insufficient. The legislative intent is to make the more radical procedures the treatment of 'last resort' . . . This is a purely medical determination, which is within a doctor's professional judgment."

The court did find, however, that the requirements that a procedure be determined to be "critically needed" for a patient's welfare was imprecise, providing no direction as to the degree of need required. In effect, the court held that the legislature had failed to provide an appropriate standard to guide those being regulated.

This became a major basis for the court's finding that AB 4481 was unconstitutional. Consequently, the "remedial" legislation, AB 1032, differentiates between psychosurgery and ECT. It requires that before psychosurgery is done "the attending physician gives adequate documentation . . . of the reasons for the procedure, that *all other appropriate treatment modalities have been exhausted* and that *this mode of treatment is definitely indicated and is the least drastic alternative available for the treatment of this patient at this time*" (emphasis added). ECT, on the other hand, may be administered only after "all reasonable treatment modalities have been carefully *considered*" (emphasis added) and ECT "is definitely indicated and is the *least drastic alternative* available for this patient at this time" (emphasis added).

Right to Privacy

The court emphasized that the right to privacy is a well-established constitutional right, which extends to the right to be free in the exercise of individual thought. Included in "individual thought" was the right to choose a medical treatment.

However, the court also declared that the regulation of "medical procedures" is "a legitimate exercise of the state's inherent police power" in order to assure that the procedures "are performed under circumstances insuring maximum safety for the patient." Medical procedures "may be regulated in different ways and to different extents" according to "their effect on the patient" and "their acceptance by the medical community." (This, of course, is one basis for regulating quackery.)

Therefore, consistent with established constitutional doctrine, the state was required to establish, first, a "compelling state interest" to justify the regulations imposed by AB 4481, and, second, that the least drastic means were employed in the process of regulation.

The court was sensitive to the dilemma posed by ECT and psychosurgery, which affect the patient's freedom of thought. Since the same dilemma may pertain to the use of sedatives, tranquilizers and other pharmacological agents which stimulate, depress or otherwise modify thinking, and to other treatment procedures which may affect thought or feeling, the court's ruling may have broader relevance to medicine.

Making an inferential reference perhaps to the 1972 vice-presidential nomination incident, the court noted that "the fact of treatment alone may impair our confidence in people of unquestioned talent and industry." It identified how "public exposure, or even disclosures to limited numbers of government representatives, may have a chilling effect on patients' efforts to undergo these treatments," thereby restricting their freedom of choice of medical treatment. Such denial of a patient's rights, said the court, must be justified by a "compelling state interest."

In applying this test, the court found that the requirement that the particulars constituting an informed consent be disclosed to a "responsible relative" violated a patient's constitutional right to privacy as well as the right to confidentiality established by statute. On the other hand, provisions requiring reporting to government officials were held constitutional because the only persons learning of the individual's identity when treatment is denied would be the patient and his attorney, conservator or guardian. This limited

infringement on the right of privacy was also deemed an effective possible remedy against abuse.

In considering the requirement that proposed treatment be reviewed by a committee of three physicians, the court noted that different criteria applied to psychosurgery and ECT. In analyzing the manner in which consent to psychosurgery is regulated, the court distinguished among patients who are incompetent, those who are involuntary and all others.

The court found that a review of a patient's competence by a review committee is constitutional where there is reason to suspect incompetence.

With respect to involuntary patients, the court described the dilemma of either prohibiting the use of psychosurgery or providing for a substitute decision-making process. Here the establishment of a review committee to make the decision for the patient was found to be justified by the state's compelling interest in preventing the involuntary administration of psychosurgery.

For patients who are found to be both competent and voluntary, the court ruled that the hazardous and experimental nature of psychosurgery justified the restraint inherent in a unanimous decision by a three-member review committee. Here the need for some restraint was held to be a sufficiently compelling interest by the state to justify the resultant invasion of the right to privacy.

Different considerations were found to apply regarding the use of a review committee for ECT. The review procedures as applied to involuntary or incompetent patients were upheld, as they provided a substitute decision-making process, deemed necessary by the court for such patients. The court also found the review process to be appropriate to assure that a candidate for ECT was both competent and voluntary. Once this decision is made, because ECT is not an experimental procedure and is not as hazardous as psychosurgery, there is less need for a substitute decision-making process. Accordingly, once it is determined that a competent informed consent can be obtained, further approval by a review committee is inappropriate. If the patient is both competent and voluntary, the patient and his physician are, in the court's opinion, best able to judge the patient's health, safety and welfare. Consequently, the requirement that a competent and voluntary patient, who has given competent informed consent, only undergo ECT upon the approval of a three-member review committee was deemed an unconstitutional invasion of privacy.

The court also concluded that AB 4481 failed adequately to provide for a hearing for patients with respect to the issues of competency and voluntariness, thereby denying procedural due process.

Due Process in AB 1032

In the "remedial" legislation, AB 1032, the due process procedures are addressed as follows:

- Quarterly reports to the state Director of Health and the local mental health director give numbers of persons involved and their legal status, consent status, age, sex and race, and the source of payment. Although the Director is permitted to identify individual treatment records, only the quarterly statistical reports are available to the state legislature or county boards of supervisors.
- Denial of rights information in the patient's treatment record may be made available to the patient or to the patient's attorney, conservator or guardian on request, but may be made available to the state legislators and county supervisors only if the identity of the patient is concealed.
- A signed and witnessed written consent form with the supplemental information shall be available to the patient and to the patient's attorney, guardian and conservator and, if the patient consents, to a responsible relative of the patient's choosing.
- Psychosurgery may only be done after a three-physician review committee has examined the patient and unanimously agreed with the attending physicians' clinical determinations and that the patient has the capacity to give informed consent.
- An involuntary patient may receive ECT only after all of the following requirements are met: (1) Documentation of the clinical indications, signed by the attending or treating physician. (2) Review of the patient's clinical record by two physicians, of whom at least one has examined the patient, with both agreeing with the treatment physician's clinical determinations. (3) The patient's written informed consent for a specified maximum number of treatments over a specified maximum period of time not to exceed 30 days, and subject to earlier written or

oral revocation by the patient. (4) Agreement by the patient's attorney or a public defender that the patient has the capacity to give a written informed consent and has done so. (5) The patient's guardian or conservator, if there is one, has been given the same oral explanation by the attending physician that the patient received.

- An involuntary patient may select a responsible relative to receive the same oral explanation that the patient receives.
- If either the attending physician or the attorney believes that an involuntary patient does not have the capacity to give a written informed consent, a petition is filed in the Superior Court and a hearing is held within three days, with the patient notified in advance, present at the hearing and represented by counsel. If the court determines that the patient does not have the capacity to give consent, the guardian or conservator or the responsible relative may give the required consent.
- A person deemed incompetent to give consent may, at any time during the course of treatment, claim regained competency, requiring that the person's competency be redetermined before treatment continues. (This provision is expected to be a major deterrent to offering ECT to involuntary patients who, because of their mental status, may interrupt after each treatment until the treatment becomes effective. Such interruptions could significantly delay treatment and prolong the risks to the patient and the course of the illness.)
- All other patients, *including those treated in a physician's office* or clinic or at home, may receive ECT only after the physician has documented in the clinical record the reasons for the treatment; a responsible relative of the patient's choosing (if the patient chooses), and the patient's guardian or conservator (if there is one), receive the same oral explanation; the patient gives written informed consent, with the limits as set forth in the five requirements for ECT listed above; and a qualified medical consultant examines the patient and verifies that the patient has the capacity to give and has given written informed consent.

To the extent that AB 1032 limits its requirements for review to the determination that the patient has the capacity to give informed consent and has done so, it would appear to have met the due process requirements set by the court. The implications are clear for all medical treatment of voluntary patients: there must be informed consent to an intrusive and hazardous procedure with "adequate documentation" of the reasons for this procedure for this patient at this time, and with qualified medical consultation, and information being given to another person of the patient's choosing, if the patient chooses. These implications are especially relevant if the procedure is likely to affect the patient's thoughts or feelings. Worth considering is the relevance to the parenteral administration of consciousness-altering drugs, such as anesthetics and sedatives, to any voluntary patient.

Right to Treatment

The court rejected the contention that there is a constitutional right to medical treatment, noting that the denial of a particular mode of treatment merely amounts to a finding that this is not a reasonable treatment, but that such a ruling does not prevent the use of alternative forms of treatment. If a patient is admitted to an institution for treatment, due process requires that "reasonable treatment" be provided or the person be released. Reasonable treatment may include alternate treatments to the clinically preferred one. Here, too, there are implications for all medical treatment of confined, or otherwise involuntary, patients.

Specialization Requirement

The court's opinion also approved the specific requirement that at least two members of the review committee be Board certified. The court reasoned that because psychosurgery is experimental, and both psychosurgery and ECT are hazardous and intrusive forms of treatment by comparison with other procedures, a higher level of competence and training is necessary.

These requirements are retained in AB 1032.

Additions in AB 1032

The newest law establishes additional limitations on ECT for minors. It totally prohibits ECT for anyone under 12 years of age. It also establishes that 16- and 17-year-old patients shall have the rights of adult mental patients, with variations as noted for incompetence or for involuntary status.

Persons 12 to 16 years of age may receive ECT only if all provisions of the law are met and the treatment is deemed appropriate, lifesaving and necessary in an emergency situation, as

unanimously certified to by a review board of three child psychiatrists. The treatment must also be reported immediately to the state Director of Health.

Intentional (intent has been added) violation of the law is now subject to a civil penalty of not more than $5,000 per violation (reduced from $10,000) and may be grounds for revocation of license.

Each licensed facility in which convulsive treatment is done must have a qualified committee to review all such treatments and the local mental health director must establish a similar review committee to audit ECT given to ambulatory patients in physicians' offices or to patients in their homes.

These requirements are significant for all of medicine. They replace professionally developed peer review and case and procedure audits with state-required audits. They apply equally to voluntary and involuntary patients and are unrelated to the payment source. In addition, this may be the first instance, other than a disciplinary matter, in which the state has legislated authority to review private office treatment of voluntary patients whose care is not being paid for by the state. The criteria justifying the exercise of the state's police power, as set forth in the court's decision on AB 4481, would appear to be:

- The procedure is sufficiently intrusive and hazardous to warrant the state's protection of the public.
- The procedure may affect thought or feeling of the recipient.

It could be said that these criteria are met by a number of medical procedures, not just psychiatric procedures, and not just those done by psychiatrists. Consequently, while the court was directly concerned with treatment of mental patients, its pronouncements are not limited to mental patients, nor are mental patients seen only by psychiatrists. Therefore, it behooves all physicians in California to be aware of the concerns expressed by the court and the legislature.

Experience Under AB 1032

In the first year under AB 1032 there were observable changes in practice, but no objective reports from either the State Department of Health or practitioners. Subjective impressions are that the administration of ECT has dropped. In some regions of the state the drop has seemed sharp; in others minimal. The decrease in ECT utilization has reflected hospital and psychiatrist policies. In several parts of California, hospitals and psychiatrists have decided to offer ECT only to voluntary patients who have the capacity to give consent. Some psychiatrists have simply discontinued administering ECT. The latter decision, they report, is in response to the combination of higher professional liability insurance, increased risk of litigation, reduced number of patients in view of hospital-imposed limitations and increased review and reporting procedures. As a result, fewer psychiatrists are accounting for all of the ECT being given in the state.

During the debate on this legislation there were allegations that ECT was not accepted by the bulk of the psychiatric profession, because only a few hundred psychiatrists accounted for most of the ECT administered in the state. The new legislation seems to have had the effect of further limiting the number of psychiatrists using this procedure. Whether this sets the stage for future further charges of overutilization and an allegation of "fringe practice" remains to be seen.

There are isolated instances of families protesting the unavailability of the procedure for relatives who benefitted from it previously but who can no longer receive it from their same psychiatrist. The numbers, however, are not known. A study of the effects on patient care is indicated.

As to psychosurgery, so little of this type of procedure was being done in California in the decade before this legislation that the effects are not expected to be great. However, here, too, no data as to the extent of psychosurgery were introduced during the legislative debate and no data have been presented since.

REFERENCES

1. AB 4481; 1974 State of California Statutes, amending State of California Welfare Institutions Code Sections 5325 and 5326, and adding Sections 5326.3, 5326.4 and 5326.5

2. Rudin E: Abstract of significant features of AB 4481 (1974 session). Central Calif Psychiatr Soc Newsletter, Oct 1974

3. State of California Welfare and Institutions Code Section 5326

4. Aden vs Younger, 57 Cal App 3d 662, 1976

5. Aden vs Younger, 58 Cal App 3d 990a; 59 Cal App 3d 174a, 1976

6. AB 1032; 1976 State of California Statutes, chap 1109; State of California and Institutions Code Section 5326.2(d)

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

BLOOD GASES IN CLINICAL PRACTICE—Leopoldo Lapuerta, MD, Chairman, Department of Medicine, Medical Director of Respiratory Therapy, Santa Rosa Medical Center, Clinical Assistant Professor, Department of Medicine, University of Texas Medical School, San Antonio. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62717), 1976. 117 pages, $12.50.

This book, clearly based on an extensive clinical experience, is directed towards the needs of those who bear clinical responsibility for patient care.

The content of the book is aptly described by the title, with the emphasis on the use of blood gas data in the interpretation of pathophysiology and in the rational management of a wide variety of respiratory diseases. The choice of material and its organization are appropriate, and the discussions are an accurate reflection of current practices in the field.

The level of sophistication of the exposition would be most appropriate for intensive-care nurses, senior medical students, and residents in surgery, internal medicine and family practice. The book could be profitably used by physicians beginning subspecialty training in pulmonary medicine as an introductory overview.

The brevity of the book, commendable in itself, necessarily results in superficiality which at times is a distinct disservice to the reader. For example, the ominous prognostic significance of hypercapnia (or even eucapnia) in an asthmatic attack is mentioned only indirectly. In the discussion of positive end-expiratory pressure (PEEP), deleterious effects such as barotrauma and reduced cardiac output are not mentioned. CPAP is defined as "Continuous Positive *Ambient* Pressure" (referring possibly to Texas hurricanes?) and its solitary appearance occurs inappropriately, in the lone paragraph devoted to ventilator weaning.

The indexer, obviously someone other than the author, has confused P_EO_2 (oxygen tension in capillary blood) with P_{CO_2} (carbon dioxide tension). The entry "Hypoxia, tissue" is followed by no less than 29 page numbers without any subheadings.

The literary style is "conversational" throughout and at times is clumsy. Nevertheless, it is always possible to follow the author's meaning, with the exception of the legend for Figure 4, which is persistently cryptic.

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* * *

ELEMENTS OF PSYCHOTHERAPY—Allen J. Enelow, MD, Professor of Health Behavior, University of the Pacific, Pacific Medical Center, San Francisco; Director, Division of Health Behavior, West Coast Cancer Foundation. Oxford University Press, 200 Madison Ave., New York City (10016), 1977. 146 pages, $8.95 (cloth), $3.95 (paper).

This short book by Dr. Enelow, who has written extensively on psychotherapy in the psychiatric literature, fills its intended purpose quite well. It is designed to appeal to any health professionals who may in their careers be engaged in psychotherapy, and although it is directed at students, it was refreshingly informative to an experienced therapist.

The book's strong points are its comprehensive description of many therapeutic techniques with the emphasis on insight oriented psychotherapy. Dr. Enelow operationally defines many terms, such as support, confrontation, interpretation and the like, which are widely used but often not well understood as concepts, even by therapists with considerable experience. In some respects, this is a practical how-to-do-it book, and while it lacks depth it is quite concise in some areas. The chapter on crisis intervention is particularly useful and this, like many of the other chapters, is illustrated with vivid case vignettes.

Certainly some of the material on group psychotherapy, which includes some of the less widely practiced forms of psychotherapy, is quite superficial; however, there are adequate references for further exploration in these areas. As Dr. Enelow rightly points out in his introduction, psychotherapy can be learned only through practice under supervision. I would suggest this book be read by all those health professionals who are beginning students of psychotherapy.

JOHN LAWALL, MD
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University of Arizona College of Medicine
Tucson

* * *

GENERAL OPHTHALMOLOGY—Eighth Edition—Daniel Vaughan, MD, Clinical Professor of Ophthalmology, University of California School of Medicine, San Francisco; and Taylor Asbury, MD, Professor of Ophthalmology, Director, Department of Ophthalmology, College of Medicine, University of Cincinnati; Illustrated by Laurel V. Schaubert. Lange Medical Publishers, Drawer L, Los Altos, CA (94022), 1977, 379 pages, $12.00.

Eight editions of *General Ophthalmology* have been produced since 1958. It is now available in Italian, Spanish, Portuguese and Polish. This is probably the ophthalmology text most widely used by medical students throughout the world. It is soft-bound, well-illustrated with photographs and diagrams, and is logically and clearly written. The selling price remains reasonable.

The text begins with lucid reviews of anatomy, embryology, and senescence. The performance of the ocular examination is reviewed. Chapter 4 provides a discussion of the principles of management of common ocular disorders, including suggestions for categories of ocular disorder requiring referral to an ophthalmologist. The remainder of the first half of the book is organized along structural lines, with chapters on each of the major anatomic elements of the eye and orbit, such as lens, retina, cornea, uveal tract and so forth.

The last half of the book is system-oriented, with chapters on such topics as neuro-opthalmology, strabismus, systemic diseases and genetic disorders. New material is presented on ultrasonography and C-T scanning. The overall length has been increased by 45 pages (to 379 pages) since the 7th edition, without sacrificing the clarity and relevance of the earlier versions. The layout is attractive, inviting the student to read onward.

This book is an outstanding aid to medical students or physicians wishing to learn about the eye and the visual system.

ROBERT S. HEPLER, MD
Professor of Ophthalmology
University of California, Los Angeles

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9:00 am	Opening Remarks
9:15 am	STRESSES OF TENNIS AND RUNNING: PREVENTION AND TREATMENT OF INJURY ..... James M. Glick, MD
9:45 am	ATHLETIC COLLISION INJURIES OF THE KNEE AND SHOULDER ..... Edward J. Greenwald, MD
10:30 am	Break
10:45 am	THE FEMALE ATHLETE ..... James M. Glick, MD
11:15 am	PANEL DISCUSSION
Noon	NSMA/Auxiliary Luncheon ..... James M. Glick, MD GAME PLAYING—THE LITTLE LEAGUER ..... Jack H. Scaff, Jr., MD
1:30 pm	THE IMMORTAL RUNNER ..... Jack H. Scaff, Jr., MD
2:15 pm	EXERCISE-INDUCED ASTHMA ..... I. Marshall Postman, MD
3:00 pm	Break
3:15 pm	HYPERPYREXIA, HEAT EXHAUSTION AND OTHER MEDICAL COMPLICATIONS OF EXERCISE .. Theodore B. Berndt, MD
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in memoriam

Baker, Thomas, San Gabriel. Died March 10, 1978 in San Gabriel of heart disease. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1944. Licensed in California in 1944. MD degree from California College of Medicine, 1962. Dr. Baker was a member of the Los Angeles County Medical Association.

Barmore, Merrill G., Whittier. Died February 14, 1978, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Dr. Barmore was a retired member of the Los Angeles County Medical Association.

Beukema, John R., Davis. Died February 7, 1978 in Sacramento of multiple bacterial infections, aged 57. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1953. Licensed in California in 1954. Dr. Beukema was a member of the Yolo County Medical Society.

Bobell, Walter M., Encino. Died March 4, 1978 in Encino of cancer of the liver, aged 47. Graduate of the University of Illinois College of Medicine, Chicago, 1954. Licensed in California in 1955.

Burrows, Ernest George, Inglewood. Died March 1, 1978 in Inglewood of heart disease, aged 66. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1939. Licensed in California in 1939. Dr. Burrows was a member of the Los Angeles County Medical Association.

Chalmers, Nate, Millbrae. Died February 3, 1978 in San Francisco, aged 59. Graduate of the University of Illinois College of Medicine, Chicago, 1945. Licensed in California in 1948. Dr. Chalmers was a member of the San Mateo County Medical Society.

Cleary, Frank W., San Mateo. Died February 1, 1978 in San Mateo, aged 60. Graduate of McGill Faculty of Medicine, Montreal, 1943. Licensed in California in 1950. Dr. Cleary was a member of the San Mateo County Medical Society.

Cohen, William P., San Francisco. Died March 18, 1978 in San Francisco, aged 47. Graduate of the University of Chicago, The School of Medicine, 1955. Licensed in California in 1956. Dr. Cohen was a member of the Alameda-Contra Costa Medical Association.

Corbin, Damon Elliott, La Jolla. Died February 22, 1978, aged 72. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1929. Licensed in California in 1930. Dr. Corbin was a retired member of the San Diego County Medical Society.

Erlwein, John F., Corte Madera. Died January 5, 1978 at Lake Tahoe of heart disease, aged 54. Graduate of St. Louis University School of Medicine, 1951. Licensed in California in 1952. Dr. Erlwein was a member of the Marin Medical Society.

Gardner, Ernest D., Davis. Died February 21, 1978, aged 63. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1941. Licensed in California in 1941. Dr. Gardner was a member of the Yolo County Medical Society.

Goodfellow, Jack, Oakland. Died February 23, 1978, aged 84. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1921. Licensed in California in 1921. MD degree from California College of Medicine, 1962. Dr. Goodfellow was a retired member of the Alameda-Contra Costa Medical Association.

Hardesty, John Thomas, Long Beach. Died February 25, 1978 in Long Beach of leukemia and diabetes, aged 67. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1934. Licensed in California in 1935. Dr. Hardesty was a member of the Los Angeles County Medical Association.

Hicks, Avery M., Menlo Park. Died March 1, 1978 at Stanford University Hospital, aged 77. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Dr. Hicks was a member of the Santa Clara County Medical Society.

Kelly, Francis A., San Jose. Died January 28, 1978 in San Jose of heart disease, aged 61. Graduate of Université de Lausanne Faculté de Médecine, 1963. Licensed in California in 1965. Dr. Kelly was a member of the Santa Clara County Medical Society.

Leach, Charles Wendell, San Francisco. Died February 20, 1978 in Greenbrae, aged 71. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Dr. Leach was a member of the San Francisco Medical Society.

Levinthal, Daniel, Beverly Hills. Died February 20, 1978 in Santa Monica, aged 83. Graduate of Chicago College of Medicine and Surgery, 1917. Licensed in California in 1944. Dr. Levinthal was a member of the Los Angeles County Medical Association.

Lipsett, Edward M., Beverly Hills. Died March 8, 1978 in Los Angeles, aged 77. Graduate of the University of Illinois College of Medicine, Chicago, 1926. Licensed in California in 1933. Dr. Lipsett was a member of the Los Angeles County Medical Association.

MAYNARD, MERLIN TREVOR-ROPER, San Jose. Died February 5, 1978, aged 80. Graduate of Washington University School of Medicine, St. Louis, 1922. Licensed in California in 1922. Dr. Maynard was a retired member of the Santa Clara County Medical Society.

MCBRIDE, ELIZABETH J., Los Angeles. Died February 9, 1978 of heart disease, aged 49. Graduate of the Medical College of Pennsylvania, Philadelphia, 1954. Licensed in California in 1958. Dr. McBride was an associate member of the Los Angeles County Medical Association.

MCKINNON, DONALD A., Sacramento. Died February 2, 1978, aged 64. Graduate of the University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Dr. McKinnon was a retired member of the Sacramento County Medical Association.

MILLER, FREDERICK J., Bakersfield. Died February 12, 1978 in Bakersfield of natural causes, aged 75. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1927. Licensed in California in 1928. Dr. Miller was a member of the Kern County Medical Society.

OSBORNE, CLYDE J., San Diego. Died March 7, 1978, aged 77. Graduate of the University of Michigan Medical School, Ann Arbor, 1924. Licensed in California in 1926. Dr. Osborne was a member of the San Diego County Medical Society.

ROSSER, BERNARD HOWARD, Los Angeles. Died January 1, 1978 in Los Angeles of acute myocardial infarction, aged 68. Graduate of the University of Southern California School of Medicine, Los Angeles, 1939. Licensed in California in 1939. Dr. Rosser was a member of the Los Angeles County Medical Association.

RUBIN, ARTHUR M., Los Angeles. Died September 17, 1977 in Los Angeles of squamous cell carcinoma of the lung, aged 67. Graduate of St. Louis University School of Medicine, 1934. Licensed in California in 1943. Dr. Rubin was a retired member of the Los Angeles County Medical Association.

SAUNDERS, JOSEPH CARVER, Los Angeles. Died October 1, 1977 in Los Angeles County of accidental drowning, aged 45. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1964. Licensed in California in 1965. Dr. Saunders was a member of the Los Angeles County Medical Association.

SZEKELY, JOSEPH L., Los Angeles. Died July 25, 1977 in Beverly Hills of carcinoma, aged 85. Graduate of the University of Medical Sciences School of Medicine, Budapest, 1915. Licensed in California in 1942. Dr. Szekely was a retired member of the Los Angeles County Medical Association.

SULLIVAN, FRANCIS J., San Francisco. Died March 28, 1978 in San Francisco, aged 45. Graduate of Cornell University Medical College, New York, 1952. Licensed in California in 1958. Dr. Sullivan was a member of the San Francisco Medical Society.

WALKIN, FRANK, Los Angeles. Died November 16, 1977 in Palm Springs of heart disease, aged 78. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1923. Licensed in California in 1946. Dr. Walkin was a member of the Los Angeles County Medical Association.

WEIL, WALTER JOSEPH, North Hollywood. Died November 27, 1977 in Vista of carcinoma, aged 72. Graduate of Deutsche Universität Medizinische Fakultät, Prague, 1934. Licensed in California in 1944. Dr. Weil was a member of the Los Angeles County Medical Association.

WILLOUGHBY, GLENN EDWARD, San Pablo. Died February 26, 1978 in Richmond, aged 56. Graduate of Ohio State University College of Medicine, Columbus, 1952. Licensed in California in 1957. Dr. Willoughby was a member of the Alameda-Contra Costa Medical Association.

ZELIGS, MEYER A., San Francisco. Died March 20, 1978 in San Francisco of carcinoma and heart disease, aged 69. Graduate of the University of Cincinnati College of Medicine, 1931. Licensed in California in 1946. Dr. Zeligs was a member of the San Francisco Medical Society.

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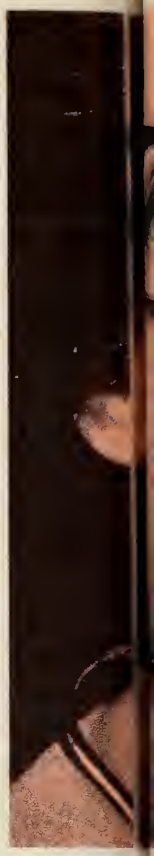

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References:

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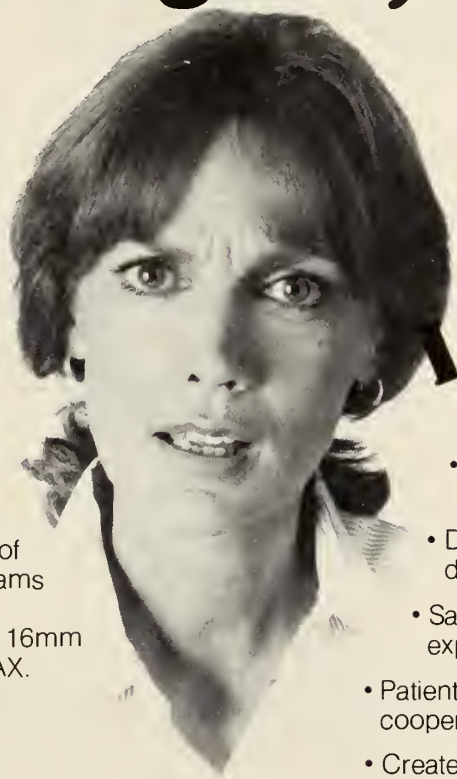

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ANESTHESIOLOGY

June 1-4—**California Society of Anesthesiologists—Annual Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401.

September 8-9—**Update of Anesthetic Drugs and Monitoring.** STAN. Friday-Saturday.

CANCER

May 20—**White Cell Separators.** San Francisco Regional Cancer Foundation at Letterman Hospital, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, S. F. Regional Cancer Foundation, 14th Ave. and Lake, San Francisco 94118. (415) 221-2132.

June 3—**Childhood Cancer Update.** PMC. Saturday. 6 hrs. $50.

June 19-23—**Head and Neck Oncology.** UCLA. Monday-Friday.

June 29-30—**Oncology Conference.** USC at Disneyland Hotel, Anaheim. Thursday-Friday.

EMERGENCY MEDICINE

June 3-4—**Critical Care Monitoring.** UCLA at Airport Marina Hotel, Marina Del Rey. Saturday-Sunday.

June 10—**Plastic Surgery for Emergency Physicians.** UCI. Saturday.

June 26-30—**Trauma—Major and Minor.** USC. Monday-Friday.

July 24-28—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $350.

August 7-11—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Islandia Hyatt House, San Diego. Monday-Friday. 40 hrs. $350.

September 11-15—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

May 16—**Common Skin Problems Seen in Office Practice.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, 199 E. Webster St., Colusa 95932. (916) 458-5844.

May 19—**American Heart Association, California Affiliate—Physicians' Scientific Sessions.** Vacation Village, San Diego. Friday. Contact: Marilyn Probst, AHA, Calif. Affiliate, 805 Burlway Rd., Burlingame 94010. (415) 342-5522.

May 19—**The Child With Heart Disease: The Practitioner's Role.** See Pediatrics, May 19.

May 19-21—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday, 13 hrs. $195. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

May 22-26—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 22-27—**Comprehensive Nephrology Review Course—3rd Biannual.** Cedars-Sinai Medical Center at Marriott Hotel, Los Angeles. Monday-Saturday. $400. Contact: Andrew J. Lewin, MD, Hypertension Research, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048.

May 29-June 2—**Advances in Internal Medicine.** UCSF. Monday-Friday.

May 31-June 2—**Advances in Child Neurology: Chronic Neurological Disorders in Childhood and Adolescence.** UCSF. Wednesday-Friday.

June 1-3—**Cardiac Symptoms and Arrhythmias—Their Diagnosis and Treatment.** International Medical Education Corp. at Marriott Inn, Marina Del Rey. Thursday-Saturday, 13 hrs. $195. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

June 3—**Infectious Disease Symposium.** Kaiser Foundation Hospital, Sacramento, at Kaiser Center, Oakland. Saturday. 5 hrs. Contact: Onera Roberts, Education Office, Kaiser Foundation Hosp., 2025 Morse Ave., Sacramento 95825. (916) 486-5965.

June 10—**Advances in Cardiology: A Practical Approach for the Primary Physician.** UCD at Waystation, South Lake Tahoe. Saturday. 7 hrs. $55.

June 10—**Flexible Fiberoptic Bronchoscopy.** PMC. Saturday. 6 hrs. $295.

June 14—**Acute and Chronic Diarrhea.** LLU. Wednesday. 4 hrs. $25.

June 15-17—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 16-18—**Coronary Disease, Exercise Testing and Rehabilitation.** International Medical Education Corp. at Inn at the Park, Anaheim. Friday-Sunday. 13 hrs. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

June 21-22—**Practical Allergy and Immunology.** USC at Beverly Wilshire Hotel, Beverly Hills. Wednesday-Thursday. 15¼ hrs. $125.

June 24—**Allergy in Office Practice.** PMC Saturday. 6 hrs. $85.

June 29—**Renal Stones.** PMC. Thursday. 6 hrs. $85.

July 28-30—**Clinical Electrocardiography and Arrhythmia Management.** International Medical Education Corp. at Newporter Inn, Newport Beach. Friday-Sunday. 13 hrs. $195. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646.

August 5—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $295.

August 9-12—**Pediatric Dermatology.** STAN. Wednesday-Saturday. 24 hrs. $225; $75, residents. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101

August 25-26—**Vascular Disease and the Brain.** Dominican Neurologic Institute and Dominican Santa Cruz Hospital. Friday-Saturday. 12 hrs. $150. Contact: Dominican Neurologic Institute, 1555 Soquel Dr., Santa Cruz 95065. (408) 476-0220, ext. 505.

August 25-27—**Dermatomycology.** UCSF. Friday-Sunday.

September 4-6—**"EEG, ABC"—13th Annual Course in Clinical Electroencephalography.** American Electroencephalographic Society at Hyatt Regency, San Francisco. Monday-Wednesday. Contact: American EEG Society Exec. Office, 38238 Glenn Ave., Willoughby, OH 44094. (216) 942-9267.

September 8-10—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton at Fishermans Wharf, San Francisco. Friday-Sunday. 13 hrs. $195. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

September 11-14—**EKG Self Assessment.** PMC and American College of Cardiology at Golden Gateway Holiday Inn, San Francisco. Monday-Thursday.

September 16-17—**Kidney Disease—18th Annual Scientific Symposium.** Kidney Foundation of Southern Calif. at Ambassador Hotel, Los Angeles. Saturday-Sunday. 8 hrs. $60. Contact: Mickie Hall Faris, KFSC, 1281 Westwood Blvd., Suite 200, Los Angeles 90024. (213) 473-6559.

September 17-21—**Pacific Dermatologic Association.** Hotel del Coronado, Coronado. Sunday-Thursday. 15½ hrs. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno NV 89509. (702) 323-2461.

(Continued on Page 34)

Brief Summary of Prescribing Information
Combined TEGOPEN® (cloxacillin sodium)
Capsules and Oral Solution
For complete information, consult Official Package Circular. (12) TEGOPEN 9/11/75

Indications: Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

Precautions: The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Adverse Reactions: Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

Usual Dosage: Adults: 250 mg. q.6h.

Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

Supplied: Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100. Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

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IN THE LOS ANGELES AREA, STAPH RESISTANCE HAS NOW REACHED 80%.*

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WHEN YOU CAN'T RULE OUT STAPH, CONSIDER

TEGOPEN®
(cloxacillin sodium)

...THE PENICILLIN OF TODAY"

- Effective against nonpenicillinase-producing staphylococci, beta-hemolytic streptococci, and pneumococci.†

†NOTE: The choice of Tegopen should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates that the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semisynthetic penicillin. The clinical significance of *in vitro* data is unknown.

- 10 times more active against strep than staph.
- Well absorbed from the G.I. tract.‡

‡Maximum absorption occurs when Tegopen is taken on an empty stomach, preferably 1-2 hrs. before meals.

Please see brief summary for prescribing information.

(Continued from Page 32)

September 28-30—**Clinical Immunology.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

September 29-October 1—**Cardiac Symptoms and Arrhythmias—Their Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $195. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

OBSTETRICS AND GYNECOLOGY

May 19—**Introduction to Colposcopy and Evaluation of Early Cervical Neoplasia.** UCD at Woodlake Inn, Sacramento. Friday. 7¼ hrs. $45.

August 26-September 1—**Practical Management of the Infertile Couple—2nd Annual Edward Tyler Symposium.** See Of Interest To All, August 26-September 1.

September 14-16—**Obstetrics and Gynecology—Annual Fall Symposium.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

September 17-23—**Advances in Obstetrics.** UCSF at Maui, Hawaii. One week.

September 21-22—**Progress in Perinatal Medicine.** Bay Area Chapter, National Foundation-March of Dimes; Kaiser-Permanente and UCSF at Hilton Hotel, San Francisco. Thursday-Friday. Contact: Arlene M. Mann, MD, Dir. of Public/Professional Ed., 1255 Post St., Suite 415, San Francisco 94109. (415) 441-1900.

September 29-30—**Office Gynecology Workshop.** PMC. Friday-Saturday. 9 hrs.

PEDIATRICS

May 19—**The Child With Heart Disease: The Practitioner's Role.** UCD at Woodlake Inn, Sacramento. Friday. 6 hrs.

May 20-21—**Neuropediatrics.** UCLA. Saturday-Sunday. 11 hrs. $165.

May 27-29—**American Academy of Pediatrics, California Chapter I, District IX.** Hyatt House, Monterey. Saturday-Monday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

May 31-June 2—**Advances in Child Neurology: Chronic Neurological Disorders in Childhood and Adolescence.** See Medicine, May 31-June 2.

June 3—**Childhood Cancer Update.** See Cancer, June 3.

June 8-9—**Pediatric Allergy and Immunology.** USC. Thursday-Friday.

August 9-12—**Pediatric Dermatology.** See Medicine, August 9-12.

September 20-21—**Brennemann Memorial Lectures—35th Annual.** Los Angeles Pediatric Society at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Los Angeles Pediatric Society, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 21-22—**Progress in Perinatal Medicine.** See Obstetrics and Gynecology, September 21-22.

PSYCHIATRY

May 19-21—**Treatment of Schizophrenia.** UCSF. Friday-Sunday.

June 2-3—**Psychosocial Care of the Dying Patient.** See Of Interest To All, June 2-3.

June 17-18—**Practical Applications of Biofeedback in the Health Sciences—5th Annual Seminar.** See Of Interest To All, June 17-18.

June 26-30—**Comparative Psychotherapies.** USC. Monday-Friday.

June 30-July 1—**Human Problems: Ordinary and Extraordinary—3rd Don D. Jackson Memorial Conference.** Mental Research Institute at Sir Francis Drake Hotel, San Francisco. Friday-Saturday. Contact: Peggy Smith, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

September 4-6—**"EEG, ABC"—13th Annual Course in Clinical Electroencephalography.** See Medicine, September 4-6.

RADIOLOGY AND PATHOLOGY

June 3-4—**Leo Rigler Radiology Symposium: Bone and Joint Radiology.** UCLA. Saturday-Sunday.

June 27-30—**Society of Nuclear Medicine—25th Annual Meeting.** Anaheim. 21 hrs. $40, members; $60, nonmembers. Contact: Margaret Glos, Exec. Dir., SNM, 475 Park Ave. S., N. Y., NY 10016. (212) 889-0717.

July 30-August 5—**Ultrasound and Computed Tomography.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Saturday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

September 9—**Gastrointestinal Radiology.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Saturday. 7 hrs. $30. Contact: Shirley Gach, Education and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4241.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

May 20-22—**Neurosurgery—8th Annual Course.** UCSF at Sheraton Palace, San Francisco. Saturday-Monday.

May 28—**Surgical Management of the Traumatized Patient—3rd Annual Clarence E. Stafford Memorial Surgical Symposium and Lecture.** White Memorial Medical Center and LLU at Bonaventure Hotel, Los Angeles. Sunday. 8½ hrs. $75. Contact: Dir. of Cont. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Box 127, Los Angeles 90033. (213) 269-9131.

June 2-3—**Intraocular Lens Implantation Course.** Santa Monica Hospital. Friday-Saturday. $600. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

June 2-4—**Soft Tissue Surgery.** USC. Friday-Saturday.

June 5-16—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1200 for otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Dir., Temporal Bone Surgical Dissection Course, ERI, 256 S. Lake St., Los Angeles 90057.

June 9-10—**Ophthalmology Update VI.** PMC at Jack Tar Hotel, San Francisco. Friday-Saturday. 13 hrs. $225.

June 10—**Strabismus Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 10—**Flexible Fiberoptic Bronchoscopy.** See Medicine, June 10.

June 11-15—**American Society of Colon and Rectal Surgeons—Annual Convention.** San Diego. Sunday-Thursday. Contact: Harriette Gibson, Admin. Sec., ASCRS, 615 Griswold, No. 516, Detroit, MI 48226. (313) 961-7880.

June 15-17—**Hip Course.** UCLA. Thursday-Saturday.

June 15-17—**Highlights of Ophthalmology.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday. 16 hrs. $195.

June 15-17—**Retina Workshop.** St. Mary's Hospital and Medical Center at Silverado Country Club, Napa. Thursday-Saturday. 12 hrs. $95. Contact: Med. Staff Secretary, St. Mary's Hosp. and Med. Ctr, 450 Stanyan St., San Francisco 94117.

June 29—**Renal Stones.** See Medicine, June 29.

August 4-5—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

September 4-6—**"EEG, ABC"—13th Annual Course in Clinical Electroencephalography.** See Medicine, September 4-6.

September 22-23—**Ophthalmology Update VII.** PMC and Update Foundation at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $225.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

May 15-21—**Diving Medicine.** UCSF at VA Hospital, Fresno. One week.

May 19-21—**Health Aspects of Human Sexuality.** Human Sexuality Program, UCSF. Friday-Sunday. Contact: John Holland, Human Sexuality Prog., UCSF, 350 Parnassus Ave., Suite 700, San Francisco 94143. (415) 666-4787.

May 20-21—**Human Sexuality.** DREW. Saturday-Sunday.

May 21-26—**Orthopaedic Symposium for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $225.

May 31-June 2—**Management of Medical Problems.** PMC at Holiday Inn on Union Square, San Francisco. Wednesday-Friday. 18 hrs. $125.

June 2-3—**Psychosocial Care of the Dying Patient.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

June 3—**Impotence: Recognizing the Causes and Treatment Options.** Eisenhower Medical Center, Rancho Mirage. Saturday. 4 hrs. $5. Contact: John J. Deller, Dir. of Education and Research, EMC, 39000 Bob Hope Dr., Rancho Mirage 92270. (714) 346-3911.

June 3-4—**Human Sexuality.** DREW. Saturday-Sunday.

June 3-4—**Nutrition: Myths and Realities.** UCSF and Institute for the Study of Human Knowledge. Saturday-Sunday.

June 7-8—**Pesticide Protection Seminar for Health Personnel.** Calif. Dept. of Health at Holiday Inn, Carmel. Wednesday-Thursday. 14 hrs. Contact: Laboratory Training Office, Dept. of Health, 2151 Berkeley Way, Room 338, Berkeley 94704. (415) 843-7900, ext. 260.

June 7-9—**Dermatology for the Family Practitioner.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Friday. 14½ hrs. $100.

June 8-10—**Metabolic and Nutritional Care of the Hospitalized Patient.** UCSF. Thursday-Saturday.

June 8-10—**Development of Occupational Medical and Safety Services.** PMC. Thursday-Saturday.

June 10-11—**Practical Infectious Diseases for the Primary Care Physician.** UCLA. Saturday-Sunday. 12 hrs. $140.

June 16-18—**San Diego Chapter, California Academy of Family Physicians—22nd Annual Postgraduate Symposium.** Town and Country Hotel, San Diego. Friday-Sunday. 15 hrs. Contact: Don Wilson, MD, 233 A St., Suite 1005, San Diego 92101.

EMPIRIN® COMPOUND c̄ CODEINE

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June 17—**Gerontological Seminar—3rd Annual.** UCSF at Diablo Valley College, Rossmoor. Saturday. 7 hrs. $50.

June 17-18—**Practical Applications of Biofeedback in the Health Sciences—5th Annual Seminar.** UCLA at Marriott Hotel, Los Angeles Airport. Saturday-Sunday. 12½ hrs. $185.

June 18-24—**Family Practice Refresher Course—9th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. Sunday-Saturday.

June 20—**Hypertension—Rationale for Appropriate Work-Up and Advances in Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

June 23-24—**Sexual Abuse: Issues for Health Practitioners.** UCSF at Sheraton Palace, San Francisco. Friday-Saturday. $80. Contact: UCSF, Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

June 30-July 1—**Human Problems: Ordinary and Extraordinary.** See Psychiatry, June 30-July 1.

July 5-August 2—**Introduction to Integral Medicine.** UCLA. Wednesday evenings. 12½ hrs. $120.

July 10-21—**Intensive Workshop in Sex Therapy Skills.** UCSF Human Sexuality Program. Two weeks. $400. Contact: Human Sexuality Program, 350 Parnassus, No. 700, San Francisco 94143. (415) 666-4787.

July 17-21—**Family Practice Refresher Course.** UCLA at Century Plaza Hotel, Los Angeles. Monday-Friday. 42½ hrs. $300.

July 22-25—**Allergy and Clinical Immunology for Non-Allergist Physicians.** American Assn. for Clinical Immunology and Allergy at Newporter Inn, Newport Beach. Saturday-Tuesday. 26 hrs. $260. Contact: AACIA, P.O. Box 912, Omaha, NE 68101. (402) 551-0801.

July 31-August 11—**Intensive Workshop in Sex Therapy Skills.** See above, July 10-21.

August 11-15—**Management of Pain.** PMC and Academy of Pain Research at Hyatt Regency, San Francisco. Friday-Tuesday. 30 hrs. $275.

August 12-23—**Annual Postgraduate Refresher Course.** USC at Hawaii. 12 days.

August 13-18—**Family Practice Refresher Course—6th Annual.** UCD at Del Monte Hyatt House, Monterey. Saturday-Thursday. 30 hrs. $225.

August 26-September 1—**Practical Management of the Infertile Couple—2nd Annual Edward Tyler Symposium.** Tyler Medical Clinic and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. 17 hrs. $150. Contact: Exclusive Travel, Inc., 3345 Wilshire Blvd., Los Angeles 90010.

September 16-17—**National Amphetamine Conference.** Amphetamine Evaluation and Physician Training Project, UCSF, Calif. Soc. for the Treatment of Alcoholism and Other Drug Dependencies, Haight-Ashbury Free Med. Clinic and CMA at UCSF. Saturday-Sunday. 11 hrs. $30, both days; $20, one day. Contact: Amphetamine Evaluation and Physician Training Project, 409 Clayton St., San Francisco 94117. (415) 626-6763.

September 23—**Drug Abuse.** UCLA. Saturday.

September 25-28—**American Academy of Family Physicians.** Brooks Hall, San Francisco. Monday-Thursday. Contact: AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

September 30-October 1—**Eight Common Clinical Problems for the Primary Care Physician.** UCLA. Saturday-Sunday.

Audio-Digest Foundation. A nonprofit educational subsidiary of the California Medical Association. Twice-a-month tape-recorded summaries of leading national meetings. Services by subscription in: Anesthesiology, Family Practice, Internal Medicine, Obstetrics/Gynecology, Ophthalmology, Otorhinolaryngology, Pediatrics, Psychiatry, Surgery. ($90.00 per year for 24 one-hour cassettes or reels.) New catalog of lectures and panel discussions in all areas of medical practice also available, as well as cassette album condensations of the following 1977 specialty meetings: postgraduate courses from the annual meeting of the American Psychiatric Assn., workshops from the annual meeting of the American College of Physicians, and postgraduate courses from the annual sessions of the American College of Obstetricians and Gynecologists. For further information on subscriptions, catalogs and special courses, contact Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

Health Research Group of the American Institutes for Research. A not-for-profit research corp. CME research project seeks physician input. Physicians in general or family practice in non-urban areas of Calif. may be contacted to participate in a major research project on development of a continuing medical education system for doctors in office practice. Project will offer, without charge, up to 30 hrs. Category I credit in return for trying out and critiquing a newly developed set of instructional materials. These materials, entitled "Management of Adult Asthma: for General and Family Physicians," and the delivery system to be tried out were developed by the Health Research Group of the American Institutes for Research under contract to the National Heart, Lung, and Blood Insitute/National Institutes of Health. Contact: Muriel H. Bagshaw, MD, Project Dir., Health Research Group, American Institutes for Research, P.O. Box 1113, Palo Alto 94302. (415) 493-3550.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470.

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

May 31-June 3—**Oregon Society of Internal Medicine and Oregon Chapter, American College of Physicians Annual Meeting.** Salishan Lodge, Gleneden Beach. Contact: Joyce Gullixson, Oregon Society of Internal Medicine, 5210 SW Corbett Avenue, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

May 17—**Circuit Course Program on Causes and Prevention of Stroke.** Presbyterian Inter-Community Hospital, Klamath Falls. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 18—**Circuit Course Program on Office Gynecology.** St. Charles Medical Center, Bend. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 18—**Circuit Course Program on Current Problems in Pediatrics.** Pacific Communities Hospital, Newport. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 25—**Circuit Course Program on Current Problems in Pediatrics.** Josephine General Hospital, Grants Pass. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

May 31—**Circuit Course Program on Disorders of the Lower G.I. Tract.** Columbia Memorial Hospital, Astoria. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Avenue, Portland 97201.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

May 19-20—**Medical Applications of Diagnostic Ultrasound.** Friday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 22-23—**Radiologic Aspects of Renal Disease—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, May 22, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, May 23, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

May 24-26—**Clinical Rheumatology—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, May 24, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, May 25, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, May 26, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

June 2—**Management of Acute Medical Problems.** Friday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. Fee: $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 5-6—**Infertility—Univ. of Wash. Obstetrics and Gynecology Program in Idaho and Washington.** Monday, June 5, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391. Tuesday, June 6, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

June 7-9—**Osteoporosis and Metabolic Bone Disease Scanning—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, June 7, Great Falls. Contact: Sidney Pratt, MD, Box 2829, Great Falls, MT 59403. (406) 453-1491. Thursday, June 8, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, June 9, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

June 8-10—**Clinical Genetics—American College of Obstetricians and Gynecologists.** Thursday-Saturday. Washington Plaza Hotel, Seattle. 25 ACOG cognates. Fee: ACOG Fellows and Junior Fellows, $175; all others, $225. Contact: Morton Stenchever, MD, Chrmn., Dept. Ob-Gyn, School of Medicine, RH-20, University of Washington, Seattle, WA 98195. (206) 543-3580.

June 26-27—**Inflammatory Bowel Disease—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, June 26, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, June 27, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

July 20-22—**Cardiology Symposium: American College of Chest Physicians—Pacific Northwest Chapter.** Thursday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

August 17-18—**Difficult Problems in Pediatric Orthopaedics.** Thursday-Friday. Washington Plaza Hotel, Seattle. 14 hrs. Fee: $150. Contact: Dept. of Orthopaedics, ZC-10, Childrens Orthopedic Hospital and Medical Center, P.O. Box C5371, Seattle, WA 98105. (206) 634-5250.

Index to The Western Journal of Medicine Advertising

Bank of America
Loans 11

Beth Israel Hospital
Aspen Mushroom Conference 29

Boehringer Ingelheim Ltd.
Catapres 8, 9, 10

Bristol Laboratories
Tegopen 32, 33

Burroughs Wellcome Co.
Empirin 35
Neosporin 21

Classified 26, 28, 29, 30

Dominican Neurologic Institute
Symposium: Vascular Disease and the Brain 27

Dorsey Laboratories
Recommendables 14, 15

Eli Lilly and Company
Darvocet-N 100 3

Endo Laboratories
Percocet 5 ..... 6, 7

Hawaiian Conference Services
Seminar in Pathology 2

Kidney Foundation of Southern California
Symposium: 18th Annual 2

Mead Johnson Laboratories
Vasodilan and Quibron 17, 18, 19, 20

Physicians & Surgeons Insurance Exchange 16

Professional Research, Inc. 25

Roche Laboratories
Dalmane 22, 23
Gantanol ..... 2nd Cover, 1, 2
Valium ..... 3rd and 4th Covers

Smith, Kline & French Co.
Dyazide 5

The Upjohn Co.
Tolinase 24

U.S. Army Recruiting Command 27

Warren-Teed Pharmaceuticals Inc.
Kaon Elixir 12, 13

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VOLUME 128 • JUNE 1978

471 *Death on Denali—Fatalities Among Climbers in Mount McKinley National Park From 1903 to 1976—Analysis of Injuries, Illnesses and Rescues in 1976*
RODMAN WILSON, MD; WILLIAM J. MILLS, JR., MD; DONALD R. ROGERS, MD, and MICHAEL T. PROPST, MD

477 *Respiration During Sleep in Children*
MARY A. CARSKADON, BA; KIM HARVEY, AB; WILLIAM C. DEMENT, MD, PhD; CHRISTIAN GUILLEMINAULT, MD; F. BLAIR SIMMONS, MD, and THOMAS F. ANDERS, MD

482 *Management of Briquet Syndrome (Hysteria)* JAMES R. MORRISON, MD

MEDICAL PROGRESS
488 *Lithium Treatment for Psychiatric Disorders* BARRY M. MALETZKY, MD, and JAMES H. SHORE, MD

SPECIALTY CONFERENCE
499 *Cerebellar Ataxia—Anatomical, Physiological and Clinical Implications*
Participants: PIERRE M. DREYFUS, MD; MEHERJI OSHTORY, MD; ERNEST D. GARDNER, MD; JAMES S. LIEBERMAN, MD; and NAZHIYATH VIJAYAN, MD
Department of Neurology, University of California, Davis, School of Medicine; and Neurology Service, Sacramento Medical Center, Sacramento

MEDICAL STAFF CONFERENCE
512 *The Ailing Health Care System*
Moderator: PHILIP R. LEE, MD; Participants: WILLIAM BRADLEY, MD; STEVEN A. SCHROEDER, MD; CRAIG LUBIN, MD; ALBERT R. JONSEN, PhD; WILLIAM B. KERR, MHA, and LEWIS H. BUTLER, Esq

IMPORTANT ADVANCES IN CLINICAL MEDICINE
527 *Plastic Surgery—Epitomes of Progress*

EDITORIALS
534 • *The Assault Upon the Professions* • *Lithium Treatment* • *The Risks of Climbing* • *Modern View of Ataxia*

CASE REPORTS
539 *Giant Sigmoid Diverticulum* RAYMOND W. WETRICH, MD, and DIP S. SIDHU, MD

542 *Esophageal Ulceration Caused by Wax-Matrix Potassium Chloride*
JEFFREY RIKER, MD; MARGO SWANSON, PharmBS, and BYRON SCHWEIGERT, PharmD

543 *Vasculitis Associated With Propylthiouracil—Evidence for Immune Complex Pathogenesis and Response to Therapy*
WILLIAM R. GRISWOLD, MD; STANLEY A. MENDOZA, MD; WILLIAM JOHNSTON, MD, and LCDR STEVEN NICHOLS, MC, USNR

CORRESPONDENCE
547 • *Success Rates in Cardiopulmonary Resuscitation* • *Local Physicians, PSRO's and HSA's* • *A New Dimension to Medicine* • *Psychogenic Rheumatism* • *Of Pediatrics and Geriatrics* • *Lincoln's Health—Dr. Schwartz Responds*

SPECIAL ARTICLE
551 *Eastern and Western Approaches to Medicine* JULIA J. TSUEI, MD

MEDICAL EDUCATION
558 *Planning Continuing Medical Education Activities* FLOYD C. PENNINGTON, PhD

566 *Volume Index*

Books Received, see Advertising Page 28

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTC ALASKA, MONTANA AND IDAHO**
(See Advertising Page 29)

★★ **Official Journal of the California Medical Associatio the Idaho Medical Association and the Nevada State Medical Association**

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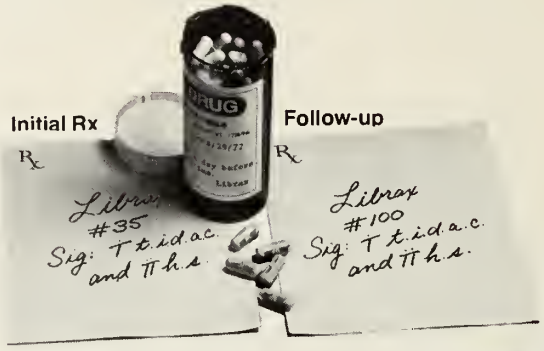

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Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

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Precautions: Potassium intoxication by oral administration rarely occurs in patients with normal kidney function, however, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

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Maximal bronchodilation with minimal cardiac effect.

More effective in exercise-induced asthma

Brethine has been shown more effective and longer-acting than metaproterenol in patients with exercise-induced asthma.[1]

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One tablet at bedtime, upon arising, and at mid-afternoon should keep patients breathing comfortably.

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If you wish to prescribe Brethine and theophylline together, the dosage of both drugs should be titrated to minimize side effects. Brethine is available in tablets of 2.5 mg and 5 mg.

Please consult the summary of prescribing information for further details.

Brethine®, brand of terbutaline sulfate, Tablets 5 mg., Tablets 2.5 mg. *Before prescribing or administering, please consult complete product information, a summary of which follows:*

Tablets contain 5 mg. (equivalent to 4.1 mg. of free base) or 2.5 mg. (equivalent to 2.05 mg. of free base) of Brethine, brand of terbutaline sulfate.

Indications: As a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Contraindications: Known hypersensitivity to sympathomimetic amines.

Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child.

Usage in Pediatrics: Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, and hyperthyroidism. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias. Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy.

Adverse Reactions: Commonly observed side effects include nervousness and tremor. Other reported reactions include headache, increased heart rate, palpitations, drowsiness, nausea, vomiting, and sweating. These reactions are generally transient in nature, usually do not require treatment, and appear to diminish in frequency with continued therapy. In general, all the side effects observed are characteristic of those commonly seen with sympathomimetic amines.

How Supplied: Round, scored, white tablets of 5 mg. in bottles of 100 and 1,000 and Unit Dose Packages of 100; oval, scored, white tablets of 2.5 mg. in bottles of 100.

(B) 98-146-060-E (Rev. 4/76)667004 C76-12

Geigy

1. Morse, J.L.C., et al: Am Rev Respir Dis *113*:89-91 (Jan.) 1976.
2. Allegra, J., et al: J Clin Pharmacol: 367-370 (July) 1976.

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MAKES SENSE

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

FOR LONG-TERM CONTROL OF HYPERTENSION.* SERUM K^+ AND BUN SHOULD BE CHECKED PERIODICALLY. (SEE WARNINGS SECTION.)

SK&F CO., Carolina, P.R. 00630

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AMERICAN COLLEGE OF CHEST PHYSICIANS

POSTGRADUATE COURSE

FALL 1978

Pulmonary Medicine

An Update for the Clinician

VAIL, COLORADO
September 18-21, 1978

Co-Sponsored by the

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Location:

The Mark
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Visiting Faculty:

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CREDIT: 19¼ hours credit toward the American Medical Association Physician's Recognition Award under Category 1.

COURSE DESCRIPTION:

The educational objective of this 3½ day course will focus on updating physicians in the field of pulmonary medicine. Emphasis will be placed on new diagnostic techniques and modes of therapy and pertinent pathophysiologic principles that will have a direct bearing on common problems encountered in pulmonary medicine. Case presentations will highlight the conference bringing out the practical aspects of certain pulmonary diseases. Ample time has been set aside for answering questions that can be submitted either in writing or orally, at each panel discussion and question and answer period.

SPECIAL SESSIONS

- Asthma
- Chronic Obstructive Pulmonary Disease
- Pulmonary Vascular Disease
- Pleural Disease
- Infectious Disease
- Diagnosis and Operability of Lung Cancer
- Hypersensitivity Lung Disease
- Mycobacterial Infection

Brief Summary of Prescribing Information
Combined TEGOPEN® (cloxacillin sodium)
Capsules and Oral Solution
For complete information, consult Official Package Circular. (12) TEGOPEN 9/11/75

Indications: Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

Precautions: The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Adverse Reactions: Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

Usual Dosage: Adults: 250 mg. q.6h.

Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

Supplied: Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100. Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

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IN THE LOS ANGELES AREA, STAPH RESISTANCE HAS NOW REACHED 80%.*

*resistance to penicillin G among community-acquired staph infections. Data on file, Bristol Laboratories.

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(cloxacillin sodium)

...THE PENICILLIN OF TODAY"

- Effective against nonpenicillinase-producing staphylococci, beta-hemolytic streptococci, and pneumococci.†

†NOTE: The choice of Tegopen should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates that the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semisynthetic penicillin. The clinical significance of *in vitro* data is unknown.

- 10 times more active against strep than staph.

- Well absorbed from the G.I. tract.‡

‡Maximum absorption occurs when Tegopen is taken on an empty stomach, preferably 1-2 hrs. before meals.

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Matter of fact, this non-dairy creamer would have been found in their home way before they ever filmed the Mocha Mix series of commercials. Steve is allergic to milk products. Yet, he likes the splash of luxury and fresh taste in his coffee, on cereal, fruit and dessert, even in cooking. For the Allen household, Mocha Mix is the perfect answer.

It could well be the answer for many people who rely on you for their dietary needs, those with an allergy similar to Steve's, or a lactose intolerance. And, for many who must maintain a fat-restricted diet you should know that Mocha Mix is one non-dairy creamer that contains no coconut oil, giving it the highest ratio of unsaturated to saturated fat of any creamer. It easily exceeds the accepted standard 2:1 ratio. It's 100% cholesterol free, too. No wonder Mocha Mix is not just another non-dairy creamer, but the one you can rely on most for your patients who can't speak for milk, either.

NUTRITION INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)
Servings Per Container 16
Calories 40
Protein ..... 0 grams
Carbohydrate ..... 3 grams
Fat ..... 3 grams
Percent of Calories from Fat 73%
Polyunsaturated Fat .. 1 gram
Saturated Fat ..... 0 grams
Cholesterol (Δ) ..... 0 mg (0 mg/100g)

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

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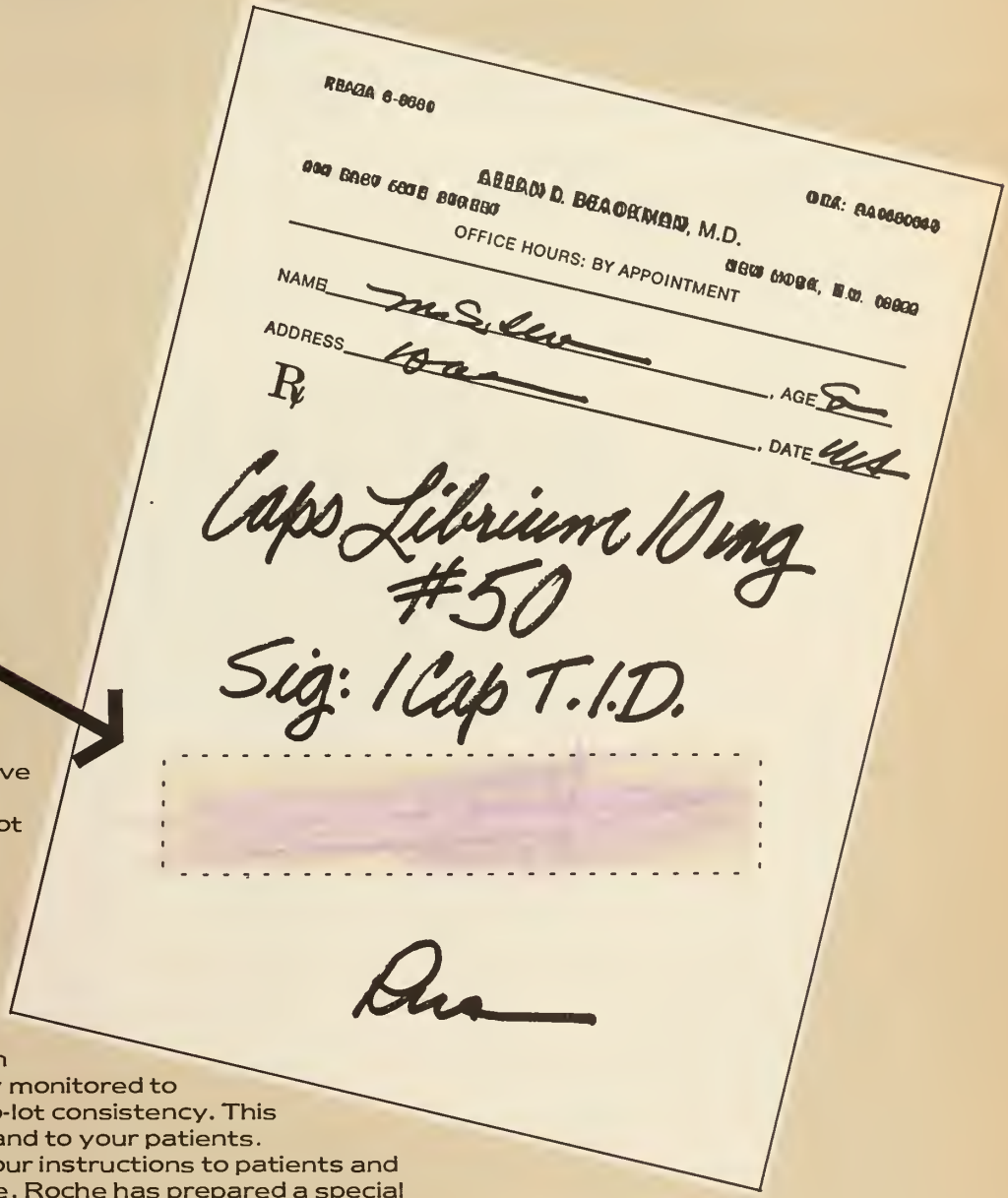
(chlordiazepoxide HCl)



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Librium sets the standards by which other chlordiazepoxides are judged. As with all Roche products, Librium manufacturing is closely monitored to assure quality and lot-to-lot consistency. This can mean a lot to you—and to your patients.

NOTE: To reinforce your instructions to patients and help improve compliance, Roche has prepared a special patient instruction sheet for Librium (chlordiazepoxide HCl). To obtain a supply, ask your Roche representative or write to Professional Services, Roche Laboratories, Nutley, New Jersey 07110.

Please see summary of product information on next page.

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chlordiazepoxide HCl/Roche

5mg, 10mg, 25mg capsules

the standard by which chlordiazepoxides are judged

Only Librium is Librium
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Unmatched experience in clinical use

Predictable patient response

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Used concomitantly with many classes of medication, such as cardiac glycosides, diuretics, antihypertensive agents, antacids and anticholinergics

Librium® ℂ IV

chlordiazepoxide HCl/Roche

5mg, 10mg, 25mg capsules

an original product of Roche research

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation; increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido –all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment, blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. Oral—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Libritabs® (chlordiazepoxide) Tablets, 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable

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COLACE prevents hard, dry stools common to constipation . . . and does it without laxative stimulation. COLACE assists peristalsis by simply letting intestinal water permeate stools.

COLACE helps to prevent painful straining at stool—particularly important in patients with delicate anorectal disorders. Safe and non-habit forming . . . COLACE, the simple water way to ease constipation from infancy to old age.

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PHARMACEUTICAL DIVISION

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- Vasodilan—compatible with coexisting diseases
- Vasodilan—compatible with concomitant therapy
- Vasodilan—compatible with your total regimen for vascular insufficiency

*Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.

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Refer to: Wilson R, Mills WJ Jr, Rogers DR, et al: Death on Denali: Fatalities among climbers in Mount McKinley National Park from 1903 to 1976—Analysis of injuries, illnesses, and rescues in 1976. West J Med 128:471-476, Jun 1978

Death on Denali

Fatalities Among Climbers in Mount McKinley National Park From 1903 to 1976—Analysis of Injuries, Illnesses and Rescues in 1976

RODMAN WILSON, MD; WILLIAM J. MILLS, JR., MD; DONALD R. ROGERS, MD, *and* MICHAEL T. PROPST, MD, *Anchorage, Alaska*

Between 1903 and 1975 about 1 percent of climbers on Mount McKinley (Denali) and Mount Foraker in Alaska died. In 1976 a total of ten (1.7 percent) of 587 mountaineers died, but this rate of death was not significantly higher than previously.

Nineteen percent of climbers in 1976 suffered major or minor injuries, illness or death. Acute mountain sickness (AMS), frostbite and fractures were common. Thirty-three rescues or retrievals of bodies were mounted at a cost of more than $82,000.

Inexperience (particularly with arctic mountaineering), poor leadership, faulty equipment and undue reliance on rescue by helicopter contributed to the alarming incidence of accident, illness and death on big peaks in Mount McKinley National Park in 1976.

MOUNTAIN CLIMBERS flock to Denali* and other high peaks in or near Mount McKinley National Park in Alaska in steadily increasing numbers. They come from around the world. Some are expert alpinists. Many are not. Most are young. All are brave. Some are foolhardy. Few have seen an arctic mountain before.

If weather is fine, over half of the climbers will reach the top of Denali because it is not a difficult ascent by some routes. Few gain the summits of nearby Mount Foraker, Mount Hunter, Mount Huntington and Mount Russell because there are no easy ways to ascend these.

Some climbers fall. Many freeze hands and feet. Some become ill with acute mountain sickness or the mundane illnesses of lowlands. Many climbers die.

Data and Reports of Cases

Table 1 lists numbers of climbers and fatalities on Denali and Mount Foraker since it is first recorded that men attempted to climb Denali in

*Denali, 6,193 m in elevation, is North America's highest mountain. It lies at 63° North Latitude 390 km from the Arctic Circle. It is officially called "Mount McKinley", but the United States Board on Geographic Names is currently considering petitions to rename the peak Denali (the tall one), an older Indian name for the mountain. Close by is Mount Foraker, 5,303 m. Both peaks are within Mount McKinley National Park.

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Submitted November 28, 1977.

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ABBREVIATIONS USED IN TEXT
AMS=acute mountain sickness
CE=cerebral edema
HAPE=high altitude pulmonary edema
RH=retinal hemorrhage

TABLE 1.—*Climbers and Deaths on Denali and Mount Foraker, 1903 to 1976**

Year	Climbers	Deaths	Year	Climbers	Deaths
1903 ...	9	0	1960 ...	37	0
1906 ...	7	0	1961 ...	32	0
1910 ...	19	0	1962 ...	40	0
1912 ...	8	0	1963 ...	50	0
1913 ...	4	0	1964 ...	33	0
1932 ...	13	2	1965 ...	31	0
1934 ...	6	0	1966 ...	22	0
1942 ...	18	0	1967 ...	83	8
1947 ...	19	0	1968 ...	40	0
1948 ...	6	0	1969 ...	71	1
1951 ...	9	0	1970 ...	124	2
1952 ...	29	0	1971 ...	163	2
1953 ...	9	0	1972 ...	181	3
1954 ...	13	1	1973 ...	203	0
1955 ...	4	0	1974 ...	302	2
1956 ...	18	0	1975 ...	381	0
1957 ...	8	0	1976 ...	587	10 (1.7%)
1958 ...	12	0			
1959 ...	8	0	Total ..	2,599	31 (1.2%)

*There were no climbers in years not listed.

1903. Data were compiled from mountaineering publications and the records of the National Park Service.* A few climbers—but probably no instances of deaths—have been missed. Two fatalities, not considered here, occurred on lesser peaks within Mount McKinley National Park, one on Red Mountain, 2,165 m, in 1973 and one on Mount Brooks, 3,140 m, in 1974.

In the 74-year period 1903 to 1976 a total of 2,599 persons tried to scale Denali or Mount Foraker. In all, 31 (1.2 percent) died—a rate of death of 12 per 1,000 climbers.

Table 2 presents deaths by principal causes. Falls on slopes killed 11 (35 percent), falls into crevasses 4 (13 percent) and an avalanche 3 (10 percent). Eight persons (26 percent) died from exposure; seven of these perished near the top of Denali in a storm in 1967.[1] Five (16 percent) have died on the mountains from high altitude cerebral edema (CE) or high altitude pulmonary edema (HAPE) or from a combination of the two.

The year 1976 was a busy and difficult one on Denali and Mount Foraker.[2,3] A record number

*Members of the Anchorage and Mount McKinley National Park offices of the National Park Service, United States Department of the Interior, supplied assistance in collecting and studying data.

TABLE 2.—*Causes of Death of Climbers on Denali and Mount Foraker, 1903 to 1976*

Cause of Death	Number of Deaths	Percent of Deaths Among Climbers
Fall on slope	11	35
Exposure	8	26
Acute mountain sickness	5	16
Cerebral edema (CE) 1		
High altitude pulmonary edema (HAPE) 2		
CE and HAPE 2		
Fall into crevasse	4	13
Avalanche	3	10
Total	31	100

of adventurers, 587, essayed the peaks. Ten (1.7 percent) died—a rate of death of 17 per 1,000 climbers. The difference between the 1976 rate and the rate of death for all previous years combined (1 percent) is, however, not statistically significant ($X^2=1.66$; $P=0.28$).

Of the ten mountaineers who died, four succumbed to falls, three were swept away by an avalanche, two died of CE or HAPE, and one died primarily from exposure. Exposure contributed to the death of two others.

Cases 1 Through 3

The deaths of three rope-mates, each from a separate cause, were intimately interrelated. They illustrate the extreme dependence of companions on one another on lofty, difficult courses.

Three Japanese alpinists were found frozen at 5,000 m on Mount Foraker by a helicopter search crew. The bodies lay in the snow with climbing rope tangled. All had superficial head abrasions and bruises. In addition one had fractured ribs, laceration of a lung, large hemothorax, rupture of a diaphragm and retroperitoneal hematoma. A second had extensive pulmonary edema. In the third no internal derangement was noted.

Comment

It is not possible to reconstruct the sequence with certainty, but it appears likely that the three fell while descending. One died because of internal bleeding. The second, perhaps ill before the fall, suffocated from HAPE. The third was left helpless high on a formidable ridge without an intact companion.

Case 4

Another man was unfortunate in other ways.

An 18-year-old youth ascended the Jungfrau, 4,158 m, in Switzerland in 1970. He noted mild

altitude sickness including headache during a night at the top. Later in the same year he went from Texas to Colorado to ski at 3,600 m elevation. After one day of skiing, intense headache, cough, dyspnea, cyanosis and vomiting developed. He had no fever. He descended by car to 1,800 m elevation and immediately recovered.

During the next five years he climbed extensively in the continental United States and Canada to 4,350 m elevation, climbed in Mexico to above 5,285 m three times, and ascended many European peaks including the Matterhorn, 4,477 m, without illness.

At age 24 in 1976 he became ill at 5,000 m elevation after climbing up onto the steep West Buttress of Denali. He was given furosemide, 40 mg intravenously, by a physician in the party but his condition deteriorated rapidly. Oxygen bottles were not available. He was lowered the next day to 4,330 m, was given more furosemide, but died with bubbling rales in his chest and bloody froth at his lips two hours after reaching the lower camp.

At autopsy the brain was very heavy, weighing 1,750 grams. It was severely edematous. White matter was extensively studded with petechial hemorrhages. Lungs weighed 1,830 grams together. Alveoli were filled with fluid which stained pink on hematoxylin and eosin preparation. Small foci of neutrophilic exudate were present in alveoli. Autopsy findings were consistent with CE and HAPE.[4,5]

Comment

In retrospect the earlier illness while skiing may also have been HAPE. Why it occurs under certain conditions of altitude and effort on one occasion and does not necessarily recur when similar or greater altitudes and degrees of effort are attained is unknown. Persons once afflicted, however, are prone as in this case to be stricken again.[6]

A total of 30 other persons suffered important injury or illness on Denali and Foraker in 1976.* All but one were examined and treated by physicians in Alaska. There were 18 cases of frostbite. Many were destructive freeze-thaw-refreeze injuries. In 11 cases hands and feet were both involved; in 5 only the feet were frozen; in 2 only the hands. No important freezing injuries to ear, nose or other parts were encountered. Four cases of hypothermia were certain; others probably occurred. There were four instances of fracture, two cases of concussion and one dislocation of a shoulder.

Illnesses included seven examples of HAPE, five of CE and six of high altitude retinal hemorrhage (RH).[7] Some cases of RH, which is usually asymptomatic, were undoubtedly missed because ocular fundi were not always examined. There were four cases of advanced dehydration, one of uncomplicated acute mountain sickness (AMS) and one of pulmonary embolism with infarction.

Two diabetic persons got into trouble: one became separated from his insulin supply and profound ketoacidosis developed but he survived after nine days in a hospital; another "deteriorated" at 4,250 m elevation when he did not take insulin which had frozen. He was removed by helicopter from 3,050 m, got insulin and recovered, but was not seen by a physician. Insulin loses little potency on freezing and thawing, but clumps may form requiring extra shaking to resuspend.[8]

Combinations of injuries and illnesses were common. Association of RH, CE and HAPE was frequent. These all may be manifestations of a single process.[9-11]

After the climbing season the National Park Service sent questionnaires to the 84 parties which had been on the mountains in 1976 asking questions about medical and other experiences. Exactly half responded. We counted 20 additional cases of mild frostbite (one person requiring admission to hospital outside Alaska for three days), 14 instances of mild AMS (the persons recovering in each case on the mountain) and two sprained ankles—a total of 36 additional disorders.

If minor injuries and illnesses occurred as often among the half not responding, then 36 more medical problems are postulated for a grand total of approximately 112 cases of injury, illness or death among 587 climbers—a rate of 191 per 1,000 (19 percent). Stated in another way, approximately one of five mountaineers suffered injury, illness or death on Denali and Mount Foraker in 1976.

Cases 5 Through 8

The fall of a rope of four illustrates the complex features of illness, injury, death and rescue on a tall and icy mountain:

A group of six men, one of whom had not climbed above 1,500 m elevation before, walked from Wonder Lake, 650 m elevation, 50 km to

*A table detailing 1976 deaths and major nonfatal illnesses and injuries is available from the authors.

the base of Denali and mounted a ridge toward the North Summit, 5,934 m. The two most experienced went on ahead over the top.

One of the four men behind got an increasingly severe headache—as if "four men at the corners of my head were pounding with sledge hammers." He also had confusion, nausea and imbalance. They left the ridge at 5,600 m elevation to descend another way, bivouacing overnight. The next day the ill man was too weak to carry his pack but managed to stagger along third in the rope. To negotiate a particularly steep pitch at 5,250 m, a belay was set with two ice axes driven deeply into snow. Ice screws, which would have been safer, were with the companions ahead. The axes loosened and the rope of four slid rapidly down a 40° couloir finally tumbling over a small ice cliff and coming to rest in a bowl at 4,950 m elevation.

How soon two died is uncertain. At autopsy of the frozen bodies several days later one of the men (case 5) had circumorbital hematomas but no brain injury, four fractured ribs, contusion of underlying lung and bilateral lower lobe atelectasis. External evidence of fractures of the hip and ankle also was noted. The other man (case 6) had only minor injuries: contusion of the forehead, contusion and laceration of the cheek, and abrasions of the nose and anterior chest. The brain was normal.

The other two were luckier. One (case 7) lay head downward on the slope, half-conscious, suspended by rope about his legs, wearing fingerless climber's gloves for 17 hours before people from another party reached him. He was first able to speak and take liquids 49 hours after the fall. One day later he was transported by helicopter from an elevation of 4,600 m to a hospital in Anchorage where he remained for one month. Injuries were concussion, suspected previous hypothermia (body temperature at hospital was 36° C [96.8°F]), subconjunctival hemorrhage, papilledema without retinal hemorrhage, deep freezing of fingers eventuating in loss of all fingers and shallow freezing of toes. In the hospital Klebsiella septicemia supervened. The patient survived.

The fourth (case 8) was conscious throughout the ordeal but was unable to help himself or his surviving companion much. He lost his hat and mittens. Help arrived, as in the case discussed above, 17 hours later. He too was removed to hospital three days after the fall. There were no residual signs of the CE which he had undoubtedly suffered before the accident. Injuries were fracture of the femur, fracture-sprain of an ankle and superficial frostbite of a foot. Recovery was good.

Comment

A combination of inexperience, poor leadership, illness and inadequate equipment led to the disastrous fall. One man (case 5) had major injuries which he might not have survived under the best of circumstances. On the mountain he had no chance. The other who died (case 6) had wounds which ordinarily would not have been mortal. He apparently had a concussion and froze before reviving.

In the course of the season on the two mountains the National Park Service arranged for evacuation by helicopter, or in two instances by small fixed-wing airplanes, of 26 persons from 15 climbing parties. This included removal of two dead persons and two tired but intact climbers who had become separated from companions. In addition three parties arranged privately for flights to remove seven other persons, four of them dead. In all, 33 of 587 (5.6 percent), or 1 of 18 climbers, required aircraft rescue. The total number of flights to the mountains is not known, but pickup was often not possible on the first pass. Landings of helicopters were above 4,100 m in all but three instances. The highest helicopter rescues were of two women from 5,950 and 5,700 m.

In a few instances victims were given oxygen in the aircraft on the way to Anchorage 215 km away, but supplemental oxygen for passengers was not usually freighted. There were no aircraft accidents. No person rescued by air subsequently died of illness or injury sustained on the mountains.

National Park Service rescues varied in cost from $250 for a small airplane trip to $15,814 for helicopter rescue of two Europeans in an operation requiring many flights. Total cost to the National Park Service was $82,200. Median cost for 15 rescues was $3,453; average cost was $3,162. Subsidy, therefore, to 587 recreationalists in 1976 was $140 each.

In summary, 40 of 587 (6.8 percent), or one of 15, mountaineers sustained major injury or illness on Denali and Mount Foraker in 1976. Ten (1.7 percent), or one of 59, died. Thirty

three (5.6 percent), or one of 18, required rescue by air. Approximately 72 other persons suffered minor injury or illness. Including these the overall rate of injury, illness or death was 19 percent, or one of five climbers.

Discussion

The death rate of climbers on Denali and Mount Foraker in 1976 of 17 per 1,000 (1.7 percent) is an appallingly high rate of death for a human activity, particularly for one which is voluntarily undertaken. It is about the same as overall mortality—18 per 1,000 (1.8 percent)—from injury and illness among the United States armed forces in wars in this century.[12]

Fatalities among climbers, however, are compressed into a few days or a few weeks on a mountain contrasted to deaths spread over months or years of military enlistment. This makes jeopardy on mountains in Mount McKinley National Park 40 to 50 times greater than that of military service during wars—more comparable perhaps to risk during an actual battle.

Since the rate of death of alpinists on Denali and Mount Foraker in 1976 was not statistically significantly greater than the rate (1 percent) in previous years combined on the same peaks, we hesitate to assert that the high number of deaths and great incidence of other injury and illness mean that climbers in 1976 were particularly unskillful or especially foolhardy.

Nonetheless, we have the suspicion, shared by old hands on Denali in 1976, that this year was, indeed, a year of unnecessary carnage. It was probably not simply an unlucky year; rather it was a season in which there seemed to be arrogance about alpine experience; prevarication about state of health on pre-climb applications to park authorities; unfamiliarity about arctic conditions; confusion about leadership; over-estimation of strength; carelessness and novel experimentation with equipment, disregard of elementary principles of mountaineering safety and hygiene, particularly with regard to hydration and to care of the feet; ignorance about AMS; casual reliance on helicopters for rescue of the ill and injured and, occasionally, of the merely fatigued, and, worst of all, callousness (with some heroic exceptions) toward the plight of parties other than one's own. If these gloomy trends continue, the outlook for future seasons is grim indeed.

It is generally agreed that the severe forms of AMS are increasingly common because people go to high places rapidly rather than hiking in from lower areas over several weeks.[13] Climbs on Denali, Foraker, Hunter and Huntington usually begin with a flight in a small airplane onto a flat spot on a glacier at an elevation of 1,500 m to 2,200 m. High altitude brain, eye and lung syndromes begin at about 2,500 m, which is scarcely above the starting point for most expeditions. Walking in from lower levels, however, does not always afford protection; CE, RH and HAPE struck one man, CE another and HAPE a third who began ascents by hiking 50 km from an elevation of 650 m to the base of Denali.

Once serious illness has come, descent is critical to survival.[14] Rescue by helicopter, if available quickly, is by far the best course, although it is hazardous and expensive. Weather was unusually fine during the climbing season on Denali and Mount Foraker in 1976. As many rescues without aircraft accident cannot be expected in a year when the weather is usual. Climbing parties, therefore, must be prepared to lower their stricken companions as soon as possible.

No one saved by helicopter or airplanes died on the way to a hospital or later. This shows how rapidly strong young persons with serious AMS recover after descending, even without oxygen being administered on the way, and how effectively major cold injuries—such as hypothermia and frozen extremities—and other trauma can be stabilized once they are admitted to hospital.[15] Rescue by helicopter is clearly the method of choice if weather and terrain allow it to be used.

Descent of the aircraft to low altitude as quickly as possible after leaving the mountain is of major importance particularly if the victim has CE or HAPE. Ideally oxygen should be administered by mask at a high rate of flow on the way to town to all seriously ill or seriously injured persons. However, if the weight of oxygen equipment compromises the ability of the aircraft to make a rescue high on a mountain or makes it impossible to rescue more than one victim, then it should be left behind. Evacuation is more important than oxygen therapy.

Adventurers will continue to engage the great mountains in Mount McKinley National Park. Injury, illness and death will inevitably come to some, but assiduous attention to party leadership,

arctic experience, climbing skill, past brushes with sickness in the mountains, equipment, hygiene, starting level of climb, rate of ascent, fall-back positions, willingness to assist others in trouble, and back-up aircraft can lessen loss of limb and life.

Addendum

Some of the lessons of 1976 may have been learned. In 1977 there were 438 persons who essayed Denali and Mount Foraker. No one died. Five were rescued by air, but the National Park Service paid ($3,369) for rescue of only two of these.

The service stationed rangers at Talkeetna, the principal staging community for climbs, and had rangers on the popular West Buttress route for periods during the season to offer advice and assistance. It was the impression of rangers that climbers were more careful in 1977 and that fewer tyros came than in 1976.

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Straining of Stools for Gallstones

A simple way to find out whether or not a patient has gallstones is to strain stools. This is a very useful way of finding out. Now, how often in the two years since my paper on the subject came out in the *New England Journal of Medicine* have I been able to persuade anybody to strain stools? Once. Nevertheless, it is something that should be kept in mind.

—HOWARD M. SPIRO, MD, *New Haven*

Extracted from *Audio-Digest Surgery,* Vol. 24, No. 7, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Carskadon MA, Harvey K, Dement WC, et al: Respiration during sleep in children. West J Med 128:477-481, Jun 1978

Respiration During Sleep in Children

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In 22 children (11 boys and 11 girls), aged 9 to 13 years, respiration was monitored during one night of sleep. No child had a significant history of breathing problems during sleep. Sleep was recorded using standard techniques (electroencephalography, electrooculography, electromyography), and respiration was measured with nasal thermistors and abdominal or thoracic strain gauges. Respiratory pauses (five seconds or longer) were determined for all sleep stages. Respiratory rate was scored only in the first and last sleep cycles and during ten waking minutes before sleep onset. Respiratory rate was significantly affected by wakefulness or stage of sleep: highest in wakefulness and stage 1, lowest in stage 2 of the last sleep cycle. Regularity of respiratory rate showed a similar effect. Variance of respiratory rate was significantly lower in girls than boys. Respiratory pauses during sleep were seen in every child, ranging from 3 to 40 pauses per night (average, 17.2 for boys and 18.0 for girls). Significantly greater numbers of pauses per minute were seen in stage 1 and rapid eye movement (REM) sleep than in stages 2, 3 and 4. The longest respiratory pause was 25 seconds. The conclusion is made that a small number of respiratory pauses during sleep are normal in children of this age.

THE ACCUMULATION of evidence linking respiratory abnormalities during sleep in infants to the sudden infant death syndrome (SIDS)[1-5] and findings of sleep-related respiratory abnormalities in adults linked to serious cardiovascular dysfunctions[6,7] have generated an increasing interest in the normal control of respiration during sleep. In addition, Guilleminault and co-workers[8,9] recently reported about a series of children who presented with a sleep apnea syndrome that was apparently related to cardiovascular abnormalities and school failure. There is also evidence in infants and adults that males are affected with SIDS or a sleep apnea syndrome in greater numbers than females.[7,10]

Because normative data on respiration during sleep in children are limited,[11] we evaluated this phenomenon in two groups of normal boys and girls to make comparisons between the sexes.

Subjects and Methods

In 22 children standard polysomnographic recording was done for one night; nasal thermistors and abdominal or thoracic mercury-filled capillary

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Submitted September 28, 1977.

This research was supported by a grant from the Spencer Foundation, grant HD 08339 from the National Institute of Child Health and Human Development, and by NIH career investigator award MH 05804 to Dr. Dement. Dr. Anders is supported by the W. T. Grant Foundation, The Robert Wood Johnson Foundation and the Boys Town Center for Youth Development at Stanford.

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ABBREVIATIONS USED IN TEXT

REM = rapid eye movement
NREM = nonrapid eye movement
SIDS = sudden infant death syndrome

strain gauges monitored respiration.

The subjects, all in good health and with normal sleeping habits, were 11 girls (aged 9 years 10 months to 13 years 2 months; average age, 12 years one month) and 11 boys (aged 10 years 3 months to 13 years 8 months; average age, 11 years 10 months). A preselected group of seven children (four girls, three boys) had a family history of narcolepsy in one parent. One of these, a girl, had complained of daytime sleepiness; another, a boy, had suffered from nightmares. Although speculation has been raised about genetic transmission patterns of narcolepsy, no firm evidence is available to support or refute this view. We, therefore, have viewed this group as a variant of normal. Laryngoscopic examination of upper airways by one of us (F.B.S.) while the subjects were awake showed no obvious malformation or obstructions in any of the children.

Data Analysis

Sleep records were scored in 30-second epochs according to standard criteria[12] in which stage 1 nonrapid eye movement (NREM) sleep is light drowsy sleep; stage 2 is spindle sleep; stages 3 and 4 are dominated by slow, high amplitude waves; and rapid eye movement (REM) sleep is characterized by low amplitude, mixed frequency electroencephalographic (EEG) patterns, bursts of rapid eye movements and suppression of skeletal muscle tonus.

Respiratory *pauses* were scored during sleep if airflow (measured by nasal thermistors) ceased for five seconds or longer. A pause was considered an *apnea* episode if airflow cessation lasted ten seconds or longer. Periodic breathing was scored if two respiratory pauses occurred within a 20-second interval.[13] Respiratory rate was counted as the number of breaths per minute and scored only during the ten minutes of wakefulness preceding sleep onset (this criterion level was not reached in six children who fell asleep in less than ten minutes), during the entire first sleep cycle (from sleep onset to the end of the first REM period), and during stage 2 and REM sleep in the last full cycle of the night. The last cycle was considered complete if the final epoch of REM sleep occurred at least ten minutes before the end of the recording.

Results

No significant differences in any of the measurements used were detected between those children with a positive family history of narcolepsy and those without. Therefore, the results for both groups were combined.

Sleep

The girls and boys spent comparable amounts of time asleep. The average total sleep time for the girls was 549.5 minutes (range, 505 to 589 minutes); the average total sleep time for the boys was 535.6 minutes (range, 458 to 577 minutes). No significant differences between boys and girls were found in the proportions of the various sleep stages.

Respiratory Rate

Respiratory rate was quite variable. The range was from a high during stage 1 sleep in one child of 21.4 breaths per minute, to a low of 12.2 breaths per minute during the last REM period in one child. Figure 1 illustrates the average difference in respiratory rate for boys and girls as a function of state. A two-factor (sex and state) repeated measures analysis of variance showed a significant effect of state ($F=9.44$; $df=6,6$; $p<.01$) on respiration rate. Respiration rate was highest during wakefulness and stage 1 and lowest during stage 2 sleep of the last cycle of the night. Although the average respiratory rate for boys was somewhat higher than for girls in every state (Figure 1), this effect was not statistically significant.

To determine the relative respiratory regularity, the standard error of the mean respiratory rate for each state in each subject was examined using a two-factor (sex and state) analysis of variance. This analysis showed that the variance for girls was consistently lower than for boys ($F=5.81$; $df=1,20$; $p<.03$). In addition, the variance was highest in wakefulness and stage 1, followed by the last REM period and the first REM period. It was lowest in stages 3 and 4 and slightly higher in the last stage 2 period ($F=6.73$; $df=6,6$; $p\leq.02$).

Respiratory Pauses

The greatest number of respiratory pauses (40) was found in one 11-year-old boy who had no prior history of snoring or respiratory problems. The fewest respiratory pauses (three) occurred in a 13-year-old girl. The average number of respiratory pauses during sleep was similar in girls (18.0 ± 8.5) and boys (17.2 ± 11.4). Figure 2 illustrates the relationship of the number of respiratory pauses to states of sleep. A two-factor (sex and state) analysis of variance was carried out. This analysis showed no effect of sex, but a significant effect of state ($F = 25.34$; $df = 3,3$; $p < .03$). The greatest number of pauses per minute occurred in stage 1, followed by approximately 50 percent fewer in REM sleep. Stages 2, 3 and 4 sleep had the fewest number of pauses per minute, averaging less than half the number seen in REM sleep.

All respiratory pauses were of the central type[14] in which airflow past the nasal thermistors and respiratory effort measured by the strain gauges ceased simultaneously. Three children had no respiratory pauses in stage 1 sleep; one had none in stage 2; four had no pauses in stages 3 and 4; and two children had none in REM sleep.

Figure 3 shows the average duration of respiratory pauses in each sleep stage. There were no significant differences in respiratory pause duration between boys and girls for any state. The duration of respiratory pauses in REM sleep was significantly shorter ($p < .01$) than in the other states. There was no significant difference in the average duration of respiratory pauses among stage 1, stage 2, and stages 3 and 4 sleep.

It is of interest that approximately 55 percent of the respiratory pauses followed a body movement. Less than three percent of the respiratory pauses preceded and seemed to initiate a body movement. The pauses that occurred before a movement were typically those of longer duration (longer than 15 seconds). Of the respiratory pauses, 42.5 percent were apneas (that is, ten seconds or longer). The longest period of apnea during sleep was 25 seconds.

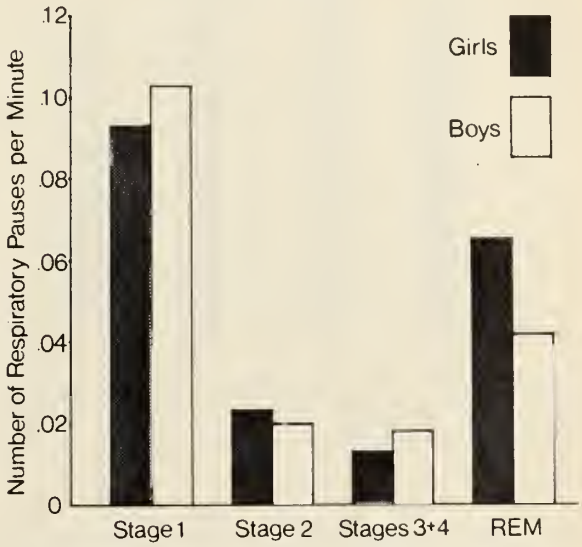

Figure 2.—Average number of respiratory pauses per minute of each sleep state as function of sex.

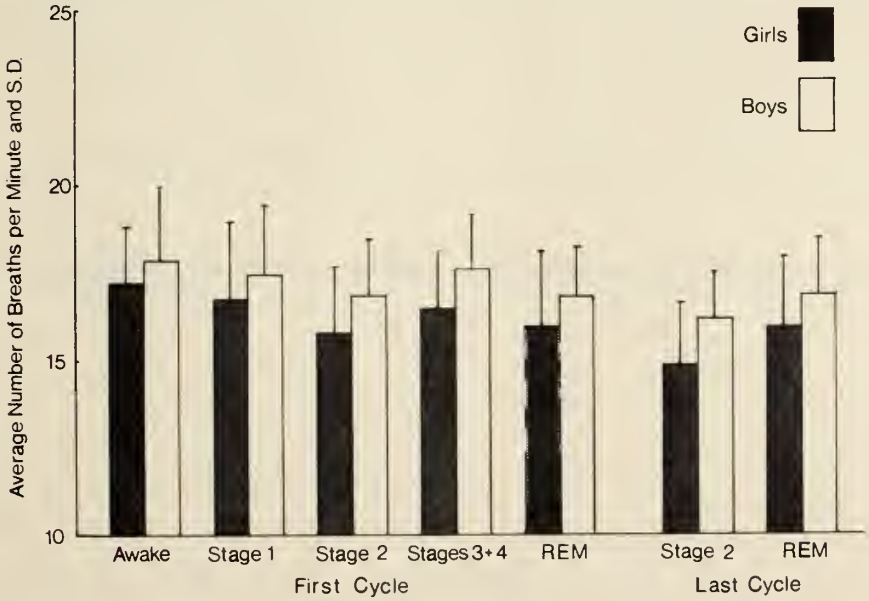

Figure 1.—Mean plus standard deviation of respiratory rate as functions of sex and sleep state.

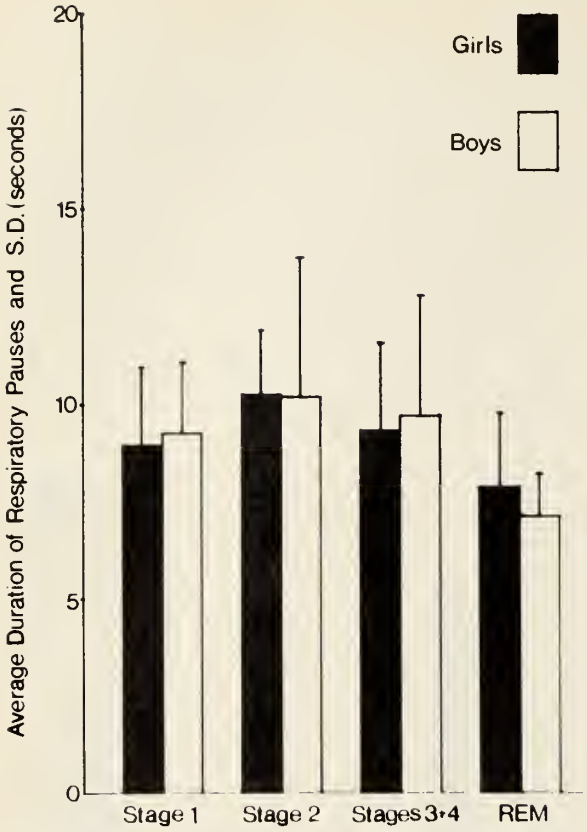

Figure 3.—Average duration plus standard deviation of duration of respiratory pauses in each sleep state as function of sex.

Periodic Breathing

Episodes of periodic breathing were uncommon; seen in only five subjects (three girls and two boys), and three of these occurred on only one occasion in REM sleep. In one boy, three brief periodic breathing episodes were seen: one in stage 4 sleep; one in stage 3 (Figure 4), and one in REM sleep. Similarly, three brief periodic breathing episodes were seen in one girl: once during stage 2 sleep and twice in REM sleep.

Discussion

None of the children had sufficient episodes of apnea to meet the criteria of a sleep apnea syndrome as defined by Guilleminault and co-workers.[7] These criteria require 30 or more *apnea* (ten seconds or longer) episodes in a night of sleep. In addition, none of the children appeared to have episodes of obstructive sleep apnea.[14] Guilhaume and Benoit[11] in their study of normal children reported an average of approximately 50 percent more apneas per child per night than in our subjects.

We conclude that it is normal for sleeping children to have apneas and respiratory pauses, probably of the central type, particularly following body movements and in REM sleep. The distribution of these respiratory pauses across

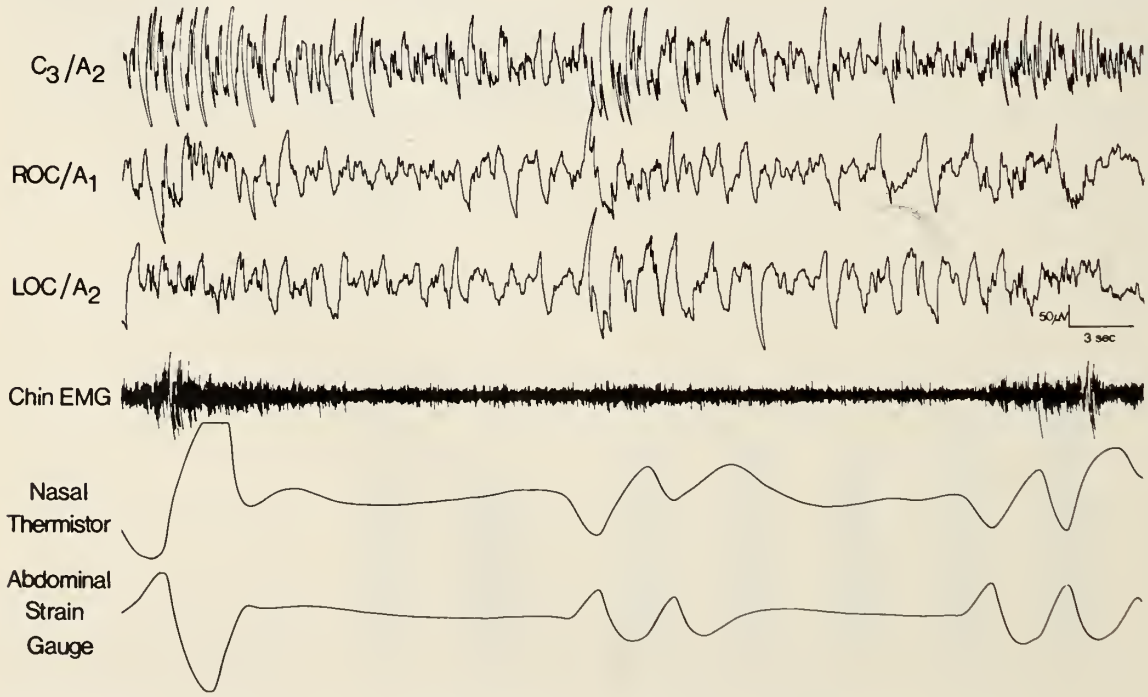

Figure 4.—Polysomnographic recording of a periodic breathing episode during slow wave sleep in an 11-year-old boy.

sleep states was consistent with findings in normal adult subjects, as was the decline in respiratory rate from beginning to end of night.[15] On the other hand, the lack of a rise in respiratory rate during REM sleep was not consistent with most studies in normal subjects.[15] This finding may reflect, however, a time of night effect. That is, while the average REM period respiratory rate in the first sleep cycle was actually lower than the respiration rate in stages 3 and 4 (in 16 subjects), the respiration rate in the last REM period was higher (15 subjects) than that in the immediately preceding stage 2.

The differences in number of apneas between men and women reported by Guilleminault and Dement[16] were not found in the children. The only difference between boys and girls was a more regular respiratory rate in girls than in boys. This finding suggest a male-female difference in the control of respiration during sleep that is not reflected in the number or duration of respiratory pauses. Our inability to show male-female differences in respiratory variables during sleep in children may reflect the prepubertal status of most of the children.

Finally, it is clear from our results that there is a vast difference in respiration during sleep between the normal children and children who have a sleep apnea syndrome.[8,9] The normal children had an average of about 18 respiratory pauses per night, with a maximum of 40 in one child, while the fewest number of apnea episodes seen in a child in whom a sleep apnea syndrome was diagnosed was 78 per night,[8] and the most as high as 816 apneas. The effectiveness of treatment in children with a sleep apnea syndrome can be readily assessed by comparison with the normative data. Guilleminault and co-workers[9] reported that in the children in whom a tracheostomy was done, the number of respiratory pauses during sleep declined to values comparable to those seen in the normal children (that is, five or six apnea episodes per night).

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Refer to: Morrison JR: Management of Briquet syndrome (hysteria). West J Med 128:482-487, Jun 1978

Management of Briquet Syndrome (Hysteria)

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The common psychiatric disorder Briquet syndrome (hysteria) has no specific treatment, but it can be managed effectively. Careful diagnosis and differentiation from other psychiatric and medical disorders is the important first step. Surgical intervention should be kept to a minimum; medicines are given cautiously and controlled carefully. The treatment of choice is supportive psychotherapy which ignores physical symptoms and encourages the patient to change the method she uses of coping with her environment.

A GENERATION AGO there was no problem; a diagnosis of hysteria meant a patient with a conversion reaction (a symptom with no evident physical cause). Either placebos were prescribed or the patient was shipped off to an analyst for psychotherapy. Neither approach benefited the patient much, but both helped the physician rid his practice of "crocks" so he could concentrate on "treating sick people."

Simple. That is the way it was for decades, until an American named Guze resurrected the work of a Frenchman named Briquet. Since then a physician facing the often thankless challenge of the hysteric patient has had a few more options in treating this tricky illness.

Diagnosis First

Any plan for management must lie upon the bedrock of a careful diagnosis. The trouble is that too many psychiatric diagnoses are too unreliable to permit planning. Conversion reaction, for example, is all but useless as a diagnosis—a third of all women have had such an experience at some time or other.[1] Investigators who follow up cases of patients with conversion reaction[2] find a variety of outcomes, including multiple sclerosis, schizophrenia, brain tumors and manic depressive disease—plus a number of perfectly healthy people, and more with "hysteria."

Even the value of hysteria as a diagnosis is diminished by the whim of individual interpretation. Some physicians equate it with conversion reaction; others relate it to a personality pattern that is dramatic, excitable and ingratiating. But many use it as a pejorative to describe unwanted behavior in their patients (or relatives). Clearly, a rational approach to treatment had to await a valid, reliable definition of the illness.

That began to come together about 20 years ago. Following earlier work of Purtell and co-workers,[3] Guze[2,4] identified an illness characterized by multiple somatic and psychiatric complaints, frequent visits to physicians and a proclivity for polysurgery, often done unnecessarily. Many of the patients involved also have the typical hysterical personality, and many have had conversion reactions as well—but neither is necessary to the diagnosis. Rather, the syndrome is described in easily understood operational terms which produce excellent agreement among independent observers (see Table 1 and accompany-

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Submitted, revised, December 19, 1977.
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ing explanation). Defined in this way, years later 90 percent or more of the patients involved retain the same diagnosis, a vast improvement over other classifications.[2]

Although Briquet described this polysymptomatic disorder 100 years ago,[5] his insight was ignored until recently. Recognizing the need to differentiate this condition from the other meanings of the term hysteria, Guze proposed the eponymous Briquet syndrome. Succinct and clinically meaningful, this term has gained some currency over the past few years, and will be used hereafter to describe these cases.

Of course, the diagnosis will never be made unless the physician is suspicious enough to ask the right questions. This should happen whenever he encounters a patient who has multiple (often vague) complaints, who bears the badge of doctor shopping (a paper bag containing a potpourri of pills), who appears to cling to ill health no matter how expert the treatment or who, with one symptom successfully treated, triumphantly returns with two more.

Family practitioners and internists probably see the bulk of these patients, although many are eventually referred to psychiatrists—in my own practice, 6 percent of adult women (in men, Briquet syndrome is virtually never diagnosed[6]) carry this diagnosis. Surgeons, too, are heavily patronized: in one study[7] hysteric patients had

TABLE 1.—*Diagnosing Briquet Syndrome*

I	1	sickly most of life
	2	headaches
II	3	blindness
	4	paralysis
	5	anesthesia
	6	aphonia
	7	convulsions or fits
	8	unconsciousness
	9	amnesia
	10	deafness
	11	hallucinations
	12	urinary retention (requiring catheterization)
	13	ataxia
	14	other pseudoneurological symptoms
III	15	fatigue
	16	lump in throat
	17	fainting spells
	18	visual blurring
	19	weakness
	20	dysuria
IV	21	dyspnea
	22	palpitations of heart
	23	anxiety attacks
	24	chest pain
	25	dizziness
V	26	anorexia
	27	abrupt weight loss
	28	frequent weight fluctuations
	29	nausea
	30	abdominal bloating
	31	food intolerance (3 or more)
	32	diarrhea
	33	constipation
VI	34	abdominal pain
	35	vomiting
VII	36	dysmenorrhea
	37	menstrual irregularity
	38	amenorrhea (2 months or more)
	39	excessive bleeding with menses
VIII	40	sexual indifference ("If I never had sex again I wouldn't care")
	41	dyspareunia
	42	other sexual problems
	43	frigidity (absence of orgasm with regular intercourse)
	44	hyperemesis gravidarum (all 9 months of pregnancy, or hospital admission for vomiting)
IX	45	back pain
	46	joint pain
	47	extremity pain
	48	burning pains of mouth, rectum, genitalia
	49	other body pains
X	50	nervousness
	51	phobias
	52	depression
	53	unable to work because of being sick
	54	crying spells
	55	hopelessness
	56	frequent thoughts of death
	57	death wishes
	58	ideas of suicide
	59	suicide attempts

This chronic illness begins by age 35, but usually in the early teens. It is diagnosed in the absence of organic pathologic conditions sufficient to explain symptoms, and if no other psychiatric diagnosis (for example, manic-depressive disease) is more likely.

For a definite diagnosis of Briquet syndrome the patient must have a dramatic, chronic illness with 25 or more symptoms in at least nine of the ten categories in the table: 20 or more symptoms in eight categories qualifies as probable Briquet syndrome.

This symptom review covers the patient's lifetime, not just the present illness. A symptom is scored positive only if the patient has seen a physician for it, taken medicine other than aspirin for it, or if it has significantly interfered with her life. Occasionally, a symptom may be scored as positive even if it does not meet one of the three foregoing criteria provided it is sufficiently impressive: a 10-minute episode of tunnel vision or paralysis may qualify, for example.

had three times more operations than controls. This illness, beginning in adolescence and persisting throughout life, probably affects 1 to 2 percent of all women and girls.[1] So from pediatricians to gerontologists, every physican can expect to encounter a number of these patients.

Having decided that his patient's symptoms are not physiological, a physician still faces a major diagnostic problem—depression. Confusion arises not only because depression plays a significant role in Briquet syndrome, but also because in some patients with depression, multiple somatic symptoms develop. In a patient in good health before an episode of depression ("this is really a change from her normal self, Doctor") tricyclic antidepressants should be tried to rule out primary affective disorder. If the patient's condition does not respond to an adequate trial (up to 300 mg per day of amitriptyline for three weeks), or if a patient bitterly complains of drowsiness after the first 25 mg tablet—a typical, but by no means pathognomonic reaction—and if the criteria for Briquet syndrome otherwise are met, then administration of antidepressants should probably be stopped. Although other treatments for endogenous depression abound, to ring the changes on all of them would take months. And by that time the patient would be thoroughly incapacitated by all the attention.

No single effective *treatment* exists for this condition. But with attention to the detail of a carefully thought-out plan, a physician can *manage* these patients effectively.

Management

Management by a physician (rather than physicians) is the first and in some ways the most important principle. It helps solve several problems.

One doctor, thoroughly familiar with his patient, can more easily judge whether a new symptom requires investigation, thereby avoiding multiple workups and inappropriate treatment. It also avoids the secondary gain—attention—the patient experiences each time she retells her story. And limiting the number of physicians curtails the patient's scope for manipulation. There is a corollary of "one patient, one doctor": the family physician or internist may be best able to provide continuing evaluation and care, using surgeons and other specialists (psychiatrists included) as consultants—sparingly.

Upon assuming care of the patient with the newly diagnosed condition, one of the physician's first tasks may be to reevaluate the forest of pill bottles with which the patient festoons his desk. Most will be unnecessary, a few potentially harmful. The latter should be discarded at once; the remainder may be eliminated outright, phased out or replaced.

Suddenly stopping administration of psychotropic drugs can backfire. Aside from the psychological dependence these people develop towards their medications, which would surely cause them to seek another physician if the drugs are discontinued abruptly, withdrawal syndromes can occur, particularly with barbiturates and tricyclics. When withdrawing medication the doctor should point out that despite the drugs the symptoms have continued, some of which may be caused by too many pills rather than too few. The patient should be told that she will not be refused medicines she really needs, but that they will be consolidated. The transition to no medicine can be eased by playing upon the pride all people feel at "doing it themselves" without pills; during this phase, more frequent visits (perhaps weekly) may be necessary.

Of course, we have to live with reality. In Briquet syndrome this means accepting the fact that some patients will continue to need medication for a while. Then it becomes the physician's job to find a drug which, above all, offers the smallest chance for abuse and side effects.

Several drugs can be excluded right away. Barbiturates and certain other hypnotics like glutethimide and chloral hydrate should be avoided because of their low safety margin and high potential for addiction. Lithium has no place in the treatment of Briquet syndrome. Antidepressants can be tried if the diagnosis is not clear, but because they are potentially lethal they should be carefully monitored or issued in small quantities (no more than a seven-day supply at a time). Phenothiazines have been popular for patients with neuroses and anxiety, but their potential for extrapyramidal side effects and tardive dyskinesia, combined with their very questionable benefit in this condition, suggests that they be used with extreme caution, if at all.

The benzodiazepines come closest to fulfilling our requirements for efficacy and safety. When given at bedtime they promote sleep, and their long half-life in the body allows the anxiolytic effect to persist well into the next day. But in

patients who need to feel more direct control over anxiety smaller doses may be required on a carefully controlled basis during the day according to circumstances. Prescriptions should be written for exact amounts needed between appointments, without refills; most patients should do reasonably well on a regimen of 20 mg per day or less of diazepam or equivalent, and the total dose should never exceed 40 mg per day. And the medication should be phased out as quickly as possible.

Dealing With Symptoms

Most symptoms can be handled best by adopting a learning theory paradigm which applies a rational system of selective attention and reward. Symptomatic behavior persists only as long as it continues to be reinforced; withdrawal of the reinforcement must be accomplished to extinguish the symptom. Hyperventilation attacks will continue as long as the family caters to the patient's wishes, rushes her to an emergency room or berates her for her misbehavior. They will diminish when ignored. This approach, which involves both hospital staff and family, may require some coordination by the physician to get underway.

This approach avoids fruitless confrontation with the patient as to whether symptoms are real or imaginary (polemics centered about this issue are not only not useful but, because they involve a reward of sorts, may reinforce the pathologic condition they seek to dismantle). It is sufficient for the patient, and should be for the physician, that her pain seems real; raising the issue that it is "all in your head" only produces mistrust or anger at the doctor. A more practical approach accepts as fact the perceived pain, but emphasizes the interpretation that anxiety (nervousness) can worsen symptoms of any stripe. The physician points out that attacking symptoms directly has not proven effective, and suggests that dealing with the problems that produce stress may be more helpful.

Not all patients respond negatively to the concept of psychosomatic causality. Some actually feel relief when given an explanation more understandable than vague viral syndromes or intangible internal disorders. A few, undeniably those with milder symptoms, are so willing to accept this explanation that they later can say, "Yes, I have anxiety attacks, pain, hyperventilation (or whatever), but the doctor told me it was just nervousness, so I don't worry about it anymore." This attitude may be fostered during psychotherapy by presenting the psychological interpretation in a positive light: "You'll feel relieved to learn that your headaches don't mean that anything is seriously wrong."

Another useful approach to symptoms is to assume that the patient will continue to have them for some time. As Jay Haley[8] explains, the perversity of human nature is such that patients try to confound physicians' expectations. If the doctor says "I suspect you will continue to be bothered by this for a while yet," she may try to defeat this prediction, too, by improving. In this manner the physician can avoid being put on the defensive, a maneuver at which his patient may be adept. If the patient continues symptomatic he can in all honesty respond, "Yes, I thought this problem might continue."

For a patient in hospital, a variant of the reward and punishment system may be used to control symptoms. A method has been described by Dickes[9] in which patients with conversion reactions are isolated and given privileges contingent upon symptom reduction. The doctor defines this approach as therapy, and tells her he is limiting her activities so she will not hurt herself. Because of this structure the patient cannot view her experience as punishment, so she must accept it without becoming angry at the physician. As affect brightens and she stops talking of suicide, she can be moved off the locked unit; further privileges accrue as improvement continues.

The disadvantage of this method is that the patient must be admitted to hospital, and that contradicts one of the overall goals of therapy in Briquet syndrome: avoid hospital admission and medical procedures. However, the magnitude of behavior in this syndrome occasionally becomes so intolerable to patient and family that a brief hospital stay must be permitted.

Sterile saline injections and sugar pills have been traditional favorites, particularly among interns and residents who find it a source of interest (and mirth) to heal the lame, the halt and the blind with briny injections. Placebos work by suggesting health to the patient so she will quickly recover from her symptom, but often unrecognized is their power to reinforce the idea that she is sick. With the possible exception of their one-time use as a diagnostic test, use of placebos should be avoided.

The attention which has now been withdrawn from somatic symptoms must be refocused else-

where. At the same time that the patient is learning to ignore symptoms about which she can do nothing, her physician should begin to focus attention upon factors she can change: the way she deals with her alcoholic husband,[10] the rearing of her hyperactive children[11] or her own drinking problem. By degrees she will learn to seek attention for talking, and recognize that she does not need somatic symptoms as a ticket of admission to the doctor's office.

Use praise early and often. At first the doctor may have to search diligently to find praiseworthy behavior, but as the patient learns to respond to verbal rewards alone she will begin to change to please her doctor. "You can be proud," he may say, "of what you have accomplished. Many patients cannot develop self-control as you have done." The physician can unabashedly use this "tincture of soft soap" approach to establish a relationship which will encourage his patient to modify her behavior. In effect, she becomes addicted to him, rather than to pills. Later he may encourage her to exercise, to enroll in classes, to find a job—all appropriate outlets for the energy which she once channeled into symptoms.

The doctor makes no attempt to control his patient's emotions; instead, he agrees with (or suggests to) her that no one can successfully control feelings. He may acknowledge her right to have feelings by saying "It is frightening to have an anxiety attack—and you are entitled to one after what you have been through." He will then go on to consider something she can change: her self-defeating behavior. Although she may be angry at her husband, she can learn not to throw dishes at him (and be praised when she reports her forbearance). As she earns praise and privileges, improvement in her self-esteem follows and she becomes eager to make further changes.

Some types of behavior must be met vigorously, and carefully. Suicide threats or attempts are foremost among these: although hysterical patients represent a small minority of completed suicides,[12] the sheer volume of attempts[13] makes an occasional success inevitable. Take no chances. Any doubt as to a patient's intentions should be resolved by hospital admission or close watch at home. Threatened or gestured suicide should be met with the same firm restrictions as any other self-defeating behavior. Seclude her "for your own good" away from activities and television, if possible on a closed ward until behavior changes for the better. Long-term inpatient care will rarely be necessary, though the promise of conservatorship or other loss of rights may be needed to rein in acting out.

The threat that a patient will change doctors if demands are not met is a ploy often used, sometimes effectively. This type of manipulation can only be met head on. First, acknowledge her power to terminate the relationship if she wishes, adding the opinion that this step would be a regrettable error, but one which the doctor would have to accept. Then leave the next step up to the patient. Occasionally, a patient will carry through her threat and depart the fold—this attrition, generally low, is necessary to avoid compromising important standards of care. Many patients who have made careers of manipulating physicians actually feel relieved when they find one who insists upon setting limits.[14]

The seductiveness often noted in these patients may present problems for a male physician who feels tempted to overreact, becoming hostile or sarcastic as he tries to maintain distance. He should carefully avoid physical contact other than a handshake, especially early in the relationship; using her title and last name (Mrs., Miss, Ms. Jones) helps maintain distance. More direct expressions of sexual interest can be met effectively by acknowledging that many patients have harmless fantasies about their doctors. With "You don't need to be afraid that I will take advantage of you," the physician permits her to have the fantasies (she will anyway) and avoids overt rejection while he informs her he will not be seduced.

The Family

Relatives can help enormously with management, provided they are educated to understand the problem. A private conference with the physician can help the spouse, parents or grown children appreciate the fact that the patient's illness, while chronic, need not be incapacitating. Although already aware that medicine does not help, many families have felt powerless to stem the flow of drugs prescribed by others. They will most likely eagerly cooperate with the "rescuing" physician as he lays out his program of drug management as described earlier. He should be cautious in interpreting the cause of this condition (although a genetic factor is suspected,[10] the complete cause remains unknown), and he should avoid using pejorative terms like hysterical and manipulation. If the family insists upon a diagnosis, Briquet syndrome does nicely. In counsel-

ing the family, stress should be laid on working *with* the patient for everyone's mutual benefit; punitiveness except in the sense of the therapeutic bind ("for your own good we must take away your privileges") must be avoided.

Although dramatic alterations in the patient's environment should be postponed (avoid abrupt changes of jobs, houses and husbands), some situations at home can be attacked directly. Alcoholism in her husband may be interrupted with family therapy and disulfiram (Antabuse®). Therapy with psychostimulants or providing reading material[15] may help a patient's hyperactive child.

The physician should encourage relatives to deal consistently with the patient, permitting no mixed messages. It may take time to learn that pills left about the house invite abuse. Relatives can most comfortably help the doctor set limits if they follow his lead in avoiding direct refusal of requests. "I can't do that (give you more medicine than is prescribed), but I can do this (talk with you about some of your anxieties)."

In working with the family, keep in mind the enormous frustrations relatives face. Living with someone who must be hauled around from doctor to doctor, who takes 15 or 20 pills a day, who cannot care for herself let alone the house or the children, and who requires frequent trips to the emergency room for overdoses and suicide gestures is enough to try the patience of a saint. The complete physician should therefore be ready to support the family in moments of crisis and to retain his perspective when relatives behave less than therapeutically.

The physician should brace himself for some pretty unpleasant feelings of his own. Conditioned as doctors are to the concept of cure, they have trouble tolerating the patient who never improves. Week after week of continuing complaints which fail to yield to his best therapeutic efforts inevitably raise feelings of inadequacy and guilt in the most competent and conscientious physician. Uncertainty as to the next therapeutic step adds to his anger, and his instinctive reaction will be to excise the patient from his practice. But if he can remember that his mission with these patients is to contain and not to cure, if he expects that for every symptom struck down two will spring up to take its place, if he can learn to expect trouble and not be disappointed when his expectations are met, then with some equanimity he can face the challenge of managing a patient with Briquet syndrome.

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Refer to: Maletzky BM, Shore JH: Lithium treatment for psychiatric disorders (Medical Progress). West J Med 128:488-498, Jun 1978

Lithium Treatment for Psychiatric Disorders

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Although used around the world since 1949, lithium has come into extensive use in psychiatry in the United States only within the past decade. Before initiating treatment with this drug, physicians must be familiar with the diagnostic scheme of the major affective disorders, the indications and contraindications to lithium's use, and its principles of treatment, including evaluation before lithium therapy, criteria for monitoring blood levels and signs of impending toxicity.

Despite earlier reports about the toxicity of lithium when it was promoted as a salt substitute, lithium is a safe drug. Its use not only has revolutionized the treatment of the major affective disorders, but has opened up new and broad avenues of research into the regulation of man's emotions.

IT IS GENERALLY ASSUMED that the present era of psychopharmacology began with the discovery of chlorpromazine (Thorazine®) in the early 1950's. It is less widely recognized that a far simpler agent, lithium, was introduced as early as 1949 for the specific disorder of mania. Lithium remains today one of our most striking yet enigmatic psychotropic drugs, its very simplicity at once intriguing and bewildering to clinicians and researchers alike. How can such an elemental substance, a mere concoction of three neutrons, protons and electrons, exert such profound effects on complex human behavior? Indeed, if such a substance does exert such effects, then might it not be a useful compass with which to explore the biology of all human emotions? Research continues today into these fascinating areas.

The purpose of the present review is to acquaint the non-psychiatric practitioner with the use of lithium in psychiatry today by tracing its development as a drug and describing its use in common and uncommon indications, the principles of its clinical employment and its associated toxicity. This review will also briefly survey the theories of lithium's mode of action and highlight important research questions remaining in elucidating lithium's effects upon the central nervous system.

History

Lithium was first identified in 1817 and isolated in 1855. It is the third element in the periodic table, the lightest of all solids, and closely

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The authors would like to dedicate this article to the memory of Paul H. Blachly, MD, who provided continuous encouragement for the study and treatment of patients with lithium therapy.

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allied chemically to sodium and potassium. During the 20th century, lithium has become an important component in the manufacture of aircraft parts, lasers and even hydrogen bombs.

In contrast to its increasing usefulness in technology, lithium has enjoyed a less consistent history in its medical applications. Medicinal springs contain the element and claims were made a century ago that such "alkaline waters" exerted a "calmative" effect.[1]

Before 1900 lithium had also been promoted as a cure for gout[2] (it dissolves urates) and was used as a sedative and anticonvulsant,[1,3] particularly as the bromide salt. With the decline of bromides, the medical community paid little attention to lithium until the late 1940's when evidence accumulated to incriminate sodium chloride as a factor in hypertension and cardiovascular disease. Manufacturers began to promote lithium chloride as the perfect salt substitute. Its unrestricted use by thousands already suffering from pathologic changes in the cardiovascular system not surprisingly prompted many reports of toxicity.[4,5] Following alarming publicity, lithium chloride was removed from the market in 1950.

The discovery by an Australian researcher, one year earlier, of lithium's usefulness in treating mania consequently went scantly heeded,[6] despite several promising confirmatory observations in the early 1950's.[7-9] It took the work of a Dane, Mogens Schou, and his group[10-12] to focus the attention of the medical world on the fact that this simplest of all drugs could exert profound effects upon manic-depressive illness.

So sharp were the memories of lithium's toxicity as a salt substitute that the drug was only approved for general use in this country as recently as 1969. Since 1960 a host of carefully documented studies has unequivocally shown its efficacy in aborting attacks of mania, preventing most manic episodes, and preventing the majority of depressive episodes from occurring as well. Its use in these conditions is considered standard in the medical community today.

Common Indications

The Affective Illnesses

The main indication for lithium's use is in those illnesses characterized by cycles of mood, both "high" and "low." Although the term bipolar in this case refers to opposite swings of mania and depression, in fact evidence indicates that these mood states may not be polar opposites at all but rather points on a continuum away from a normal mood state, mania being more distant than depression.

The manic state is typified by signs of overactivity and gregariousness. The manic, under the sway of an attack, hardly feels ill at all but rather feels marvelously well, indeed euphoric. Never still and rarely quiet, he constantly seeks out and accepts new tasks beyond his capacities. His judgment atrophied, he invests money unwisely, occasionally becoming inappropriately expansive in donating his last penny to some charity or friend. He has no time for sleep, perhaps averaging two to three hours each night, and may either eat little or consume enormous quantities of food. His appetite may also be aroused for sexual gratification and hypersexual "binges" are not uncommon. His emotions are labile and his verbal associations flighty. He is distractible and despite claims that he feels "on top of the world" he may nevertheless be irritable, argumentative and even volatile at times, especially when crossed. He may develop ideas of grandiosity. Needless to say, the manic patient quickly exhausts emotional and physical resources of family and friends and in full-blown mania he usually comes to psychiatric attention.

Often more destructive and insidious is the condition of hypomania in which many of the symptoms described above occur but in attenuated form. The hypomanic patient rarely can be convinced he is in need of medical attention, yet rarely will anyone coerce him to accept such treatment, as his symptoms seem but an exaggerated form of normality. Nevertheless, he continues to place an emotional and financial drain on his family. The condition may persist for months.

The state of depression is a less well-defined condition. The patient usually expresses feelings of hopelessness and pessimism. He may believe he is responsible for some wrongdoing, consequently suffering extreme guilt, or he may develop delusions about a bodily illness. He may move slowly, sitting rigidly with head and eyes downcast, or may not be able to sit or stand quietly at all but rather pace back and forth, wringing his hands, shaking his head and nervously clenching his teeth. He shuns social contacts, finds no pleasure in former recreations and indeed can

hardly express any emotion at all except sadness. He may have trouble concentrating and be slow to respond. When he does he may utter but brief statements as if the effort were hardly worthwhile. He will usually have difficulty sleeping, particularly in the early morning hours, and may have lost weight because of a pronounced diminution in appetite. Sexual desire is similarly reduced.

Some manic-depressive patients alternate between episodes of mania and states of depression interspersed with periods of relative normality. Such patients are called manic-depressive cyclical type (bipolar illness). Other patients experience only manic episodes, the manic-depressive, manic type, while still others show only the depressed phases and are called "unipolar." The terminology is confusing at best. Some recent research indicates, in fact, that unipolar and bipolar illnesses can be differentiated on clinical,[13-15] biochemical[16-18] and genetic grounds.

Manic-depressive psychosis usually begins at an older age than schizophrenia and most writers sharply differentiate between these two syndromes. The manic lacks a well-formed delusional system and rarely hallucinates. He does not display the grossly illogical and bizarre thought patterns of the schizophrenic, and usually is able to preserve congruent emotional responses. Nonetheless, diagnostic boundaries between the two cannot always be sharply drawn.

There is evidence that bipolar mood states and indeed almost all lithium-sensitive disorders are related in part to genetic[15] and biochemical[17] abnormalities affecting the central nervous system. These endogenous disorders are to be differentiated from clearly exogenous conditions in which externally stressful agents are primary. Therefore, lithium may be very effective in patients with severe mood swings unconnected to changes in the immediate environment but would have no place in the treatment of patients with depression secondary to, for example, a divorce or a death in the family.

Acute Mania

For years the phenothiazines, especialy chlorpromazine, were prescribed for acutely manic patients, and for good reason: such a patient not only could exhaust others with his behavior, he could exhaust himself as well. The phenothiazines were effective in calming the patient within 24 to 72 hours but they rarely seemed to alter the basic symptomatology or course of the disease; many assumed they merely muffled manic symptoms until a natural remission occurred.

A multitude of uncontrolled and controlled studies[19-29] have now documented lithium's efficacy in aborting acute manic attacks. In dosages ranging from 900 to 1,800 mg per day, lithium will almost invariably end manic episodes within four to ten days. (For more extensive recommendations regarding dosage and the monitoring of serum lithium levels, see "Principles of Treatment" later in this review.) It must be emphasized, however, that four to ten days may be too long to allow such an episode to go unchecked. Many authorities recommend the adjunctive use of a phenothiazine, typically chlorpromazine or haloperidol, to more quickly sedate the patient while lithium is beginning to take effect. Almost always the phenothiazine can be discontinued once this has occurred.

With the use of lithium in this manner one notices a qualitatively different remission than that formerly produced by the phenothiazines alone. The patient is not unduly sedated; he is calmer and less hyperactive, and in a truly stabilized mood rather than a suppressed condition. Lithium has appeared to produce a truly *normalizing* as opposed to a *tranquilizing* effect.

Prophylactic Lithium

Perhaps even surpassing lithium's dramatic effect in the treatment of mania is its efficacy in *preventing* further episodes of mania or depression in bipolar patients. Some of psychiatry's most elegant studies have clearly shown this prophylactic effect,[30-33] one which has revolutionized the treatment of manic-depressive illness in the past decade. Moreover, lithium exerts its prophylactic effect even against recurrences of depression as well as mania, although to a slightly less significant degree. Figure 1, taken from an early study by Furlong and associates,[34] convincingly shows this ability to prevent further episodes of both mania and depression. It should be noted that this prophylactic effect may not become evident for six months or more; patients must be cautioned not to expect immediate responses.

Recently a variety of manic-depressive patients with rapid fluctuations of mood, generally stated in terms of hours or days, as opposed to weeks or months, has been described. Such rapid cycles usually do not respond as well to lithium, though further study is warranted.[35]

When used prophylactically, less lithium is usually required. Though 900 mg per day has been regarded as a standard maintenance dose, 600 mg and even 300 mg have been reported effective in occasional patients.[36] Individually tailoring the dosage by monitoring serum lithium levels and clinical responses can permit a wide range of dosages to be employed.

While the manic-depressive patient continuously taking lithium may appear "normalized," minor mood swings, especially depressions, can occur. These occasionally may require the addition of an antidepressant. Even after many years a patient can suffer a relapse should the drug be discontinued. Therefore while lithium may be prophylactic it is obviously not curative for manic-depression. Most authorities now agree that once the diagnosis of manic-depressive disorder is certain (usually more than one manic or depressive episode is required), lithium should be continued indefinitely.

Acute Depression

Because lithium can prevent the occurrence of a depressive episode in manic-depressive disorders, it is natural to assume that the drug can also lift a manic-depressive patient out of a depression. Unfortunately, this is not always so. Patients encountered in a depression but known to be bipolar may require an antidepressant medication at first to alleviate the depression. Lithium only rarely produces or aggravates a preexisting depression. Therefore, frequently an antidepressant is administered along with lithium

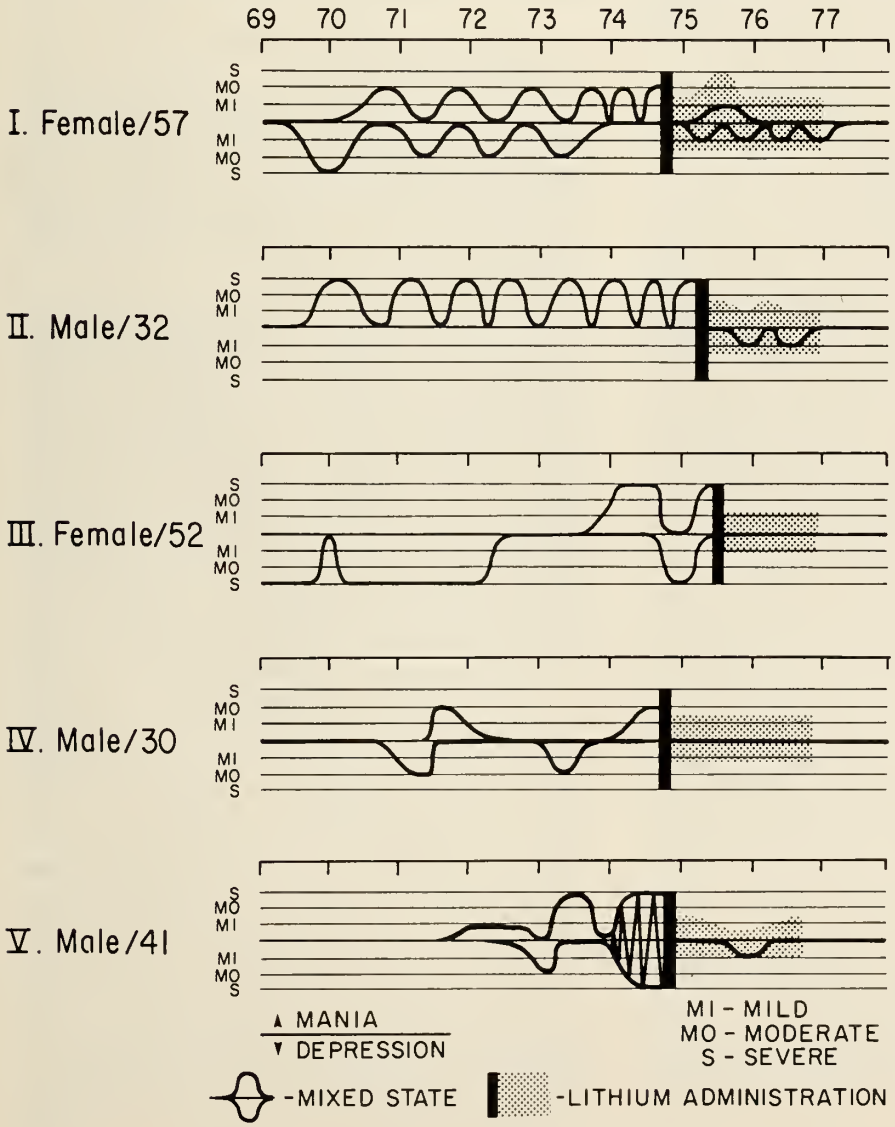

Figure 1.—Response to affective attacks with lithium (Reproduced with permission from the *Canadian Psychiatric Association Journal* 13:489, 1968).

TABLE 1.—*Factors Associated with an Antidepressant Response to Lithium*

History of bipolarity.
Family history of bipolarity.
Endogenous symptom pattern.
Increased average evoked responses.
High erythrocyte lithium: plasma lithium ratio.
High plasma calcium: magnesium ratio.
Initial increase in plasma calcium and magnesium with lithium treatment.
Reduced accumulation of 5-hydroxyindole acetic acid in lumbar spinal fluid.
Reduced erythrocyte catechol-o-methyl transferase levels.

in the depressed phase of a bipolar illness, so that the lithium has a "head start" in preventing any further affective episodes.

A significant problem in evaluating lithium's effect in treating acute depressions and preventing repeated depressions is the diagnosis of depression itself. A confusing array of terms has been applied to the clinical conditions of sadness we treat. We must differentiate between *exogenous* conditions, those that stem directly from external losses, and *endogenous* ones, those that seem to have a life of their own and probably stem, in the main, from genetic and biochemical factors.

A review of the evidence now indicates that lithium is certainly not the drug of choice in the midst of an endogenous depression.[37,38] Certainly a tricyclic antidepressant, such as amitriptyline or imipramine, would form the first choice in such treatment. Neither would lithium be used in the postpartum or involutional depressions. Evidence here is too scanty to make a firm decision but other antidepressants and electroconvulsive therapy (ECT) have proven more effective in these conditions. However, there is evidence that lithium exerts some antidepressant effect in acute depressions. Six of nine uncontrolled studies and eight of 11 controlled studies show some such effect, though occasionally weak.[39] Clinically we have almost always used an antidepressant or ECT in cases of acute endogenous depressions, even those we knew were bipolar, but more and more often now, because of the above evidence, we are considering lithium after failure of the usual antidepressants or electroconvulsive therapy, or both.

Which acutely depressed patients will respond to lithium treatment? Table 1 lists those characteristics that now help us predict which patients will respond to therapy with lithium. Certainly a history of bipolarity helps and this seems to fit into a coherent whole: bipolarity is a lithium-responsive condition;[40] but bipolarity is not always readily apparent. Is a patient with a first depressive episode going to have further depressions (making him "unipolar") or some manic episodes too (making him "bipolar")? There are no means now to predict for certain but a family genetic history is all too frequently overlooked as a valuable aid. Those with a history of bipolarity in their family, or with the history of a family member who responded to lithium, stand a good chance of a positive response to the drug. Most exciting also is the surge of interest now in chemical predictors of drug response. Already serum urine and spinal fluid monamine metabolites can help us choose which antidepressant[14,16,41] to use; there are indications they may also help to predict response to lithium in the near future.

Prophylaxis in Unipolar Recurrent Depression

Patients with unipolar recurrent depressions form one of the largest groups seen clinically in a medical or psychiatric practice, considerably exceeding the number of bipolar patients. Therapy with lithium does not relieve these acute depressions well, but does it prevent them from recurring?

Data indicate that the tricyclic antidepressants are superior to lithium in the prevention of depression in this illness but that lithium does have some preventive effect.[42-44] A study involving 12 Veterans Administration hospitals found that adequate levels of lithium (greater than 1,000 mg per day, serum levels maintained between 0.8 and 1.0 mEq per liter) were associated with good prophylaxis against the return of a depression.[38] The problem is that imipramine, a tricyclic antidepressant, produced even better results, though the difference was not significant.

These data are typical and make us hesitant to use lithium continuously to prevent depressions in the absence of a known history of bipolarity. While the use of lithium is certainly as safe as that of an antidepressant, its toxic:therapeutic ratio is less and it requires more careful monitoring. There is excellent evidence, as previously stated, that the unipolar recurrent depressions differ from the bipolar manic and depressive conditions genetically, epidemiologically, chemically and clinically. The fact that lithium exerts *some* effect in preventing these depressions, however, would argue for some basic biochemical

mechanism regulating affect which may be disturbed in both conditions. Hence lithium promises to be an exciting tool with which to explore mood itself, regardless of its direction.

Uncommon Indications

Schizophrenia

The borders between the schizophrenic and affective disorders are hazily drawn in certain cases. Some would assert that those mixed cases of schizophrenia and manic-depressive disorder are points on a continuum. The term schizoaffective schizophrenia, coined decades ago, underscores our confusion in diagnosing those with depressive or manic symptoms in concert with loose associations, inappropriate emotional responses, bizarre ideation, suspiciousness, posturing, delusions and hallucinations.

When lithium's use in such patients is compared with use of a phenothiazine, the common choice in all schizophrenic conditions, conflicting reports occur. Most studies find *some* value in the use of lithium with schizoaffective patients, especially in decreasing the "affective" component: pressured speech, excitability, delusions of grandeur, sadness.[22,45,46] However, lithium does not consistently reduce peculiarly schizophrenic symptoms such as hallucinations and loose associations;[45-48] occasionally it can aggravate a schizophrenic episode by producing additional confusion and disorientation.[28,37]

At present lithium's use in schizophrenia should be restricted to those patients with affective signs predominating. It should usually be combined with a phenothiazine. Evidence is clear that it is not effective in schizophrenic subtypes other than the schizoaffective.[49] One beneficial byproduct of lithium's occasional efficacy in schizoaffective patients is the realization that many patients we thought had a schizophrenic, and hence deteriorating, course actually have an affective illness with a better prognosis. Those with good premorbid history, lack of schizophrenia in relatives, sudden onset, brief episodes and return to premorbid functioning level may have in fact suffered a manic-depressive illness, not schizophrenia, even though thought confusion, delusions and hallucinations were present.

Premenstrual Tension

The premenstrual tension syndrome is marked by both affective symptomatology and periodicity. Hence it was logical to test lithium for this condition. Several studies have hinted at its usefulness but few patients have been reported.[50-53] Lithium is, however, widely used clinically in this condition with fair results. A controlled trial would be of interest, especially one comparing lithium with diuretics, the other major treatment modality.

Hyperactive Children

Children who cannot sit still or concentrate in school share some similarities with overactive manic patients. Hence lithium was tested early in the hyperkinetic syndrome. Initial reports[54-57] were promising but some later reports have been equivocal. Those children responding are said to be actually manic-depressive and some infer a diagnosis of manic-depression in all overactive children.[58] Those with family histories of manic-depression are most often responsive.

One must view these results with caution in the face of overwhelming evidence of the beneficial effects of stimulants in this syndrome. Lithium can produce lassitude in normals—is this the source of benefit in hyperactive children or is a more specific effect present? At present, though lithium offers no special risk to children, it would be best to restrict its use in this syndrome to those refractory to stimulants or tricyclics, to neuroleptics and in behavioral techniques.

Syndromes of Violence

Manic patients are not always euphoric or even happy. Often, when crossed, they are irritable, even violent. Lithium's normalizing effect in these patients made it a reasonable choice to treat certain character disorders marked by violence.

Several studies have shown lithium's efficacy in decreasing episodes of violence and aggression.[59-63] Some of these studies employed prisoners and acts of aggression were tallied by prison personnel. It is as yet unclear whether lithium's nonspecific action in diminishing activity or any specific antiagressive actions were responsible.

Whether lithium will be helpful in alleviating clinical syndromes associated with violence is unclear. Many patients are seen in clinical practice with symptoms of "episodic violent character disorders," including mood swings of brief duration and labile quality, drug abuse, violence and impulsivity. Quitman has found lithium better than placebo in treating such patients,[64] though this result cries out for confirmation. Lithium has

yet to be used in the episodic dyscontrol syndrome though Sheard's violent prisoners,[59] responding positively to lithium, possibly included a number of such explosive patients.

At our present state of knowledge, referral to a psychiatrist for a combination of medications and psychotherapeutic procedures would seem the most appropriate form of treatment for the potentially or actively violent patient.

Miscellaneous

Anecdotal reports of lithium's helpful effect in epilepsy[64,65] have not been confirmed by general clinical practice. Similarly, early reports that lithium resulted in the diminished craving for alcohol have not, unfortunately, been verified.[66] Uncontrolled and controlled observations suggest some benefit from lithium in obsessional states.[64]

Lithium bears testing in these and other neuropsychiatric conditions in part because of the uncertainty of our nosologic scheme. Perhaps many of the conditions we treat reflect aberrations within a basic affective regulatory system; perhaps lithium exerts a normalizing role regardless of the defect. Lithium can be shown to protect against the recurrence of many "periodic" psychoses, such as the regularly recurring catatonias or confusional states previously lumped under the schizophrenic rubric.[67,68] The drug, therefore, may exert protection against "dysrhythmia" and restore homeostasis in what were considered widely disparate conditions.

Nonetheless in clinical practice lithium's use currently is most often reserved for the affective disorders as previously mentioned. Its status in the treatment of the schizophrenias and the other conditions cited above, while not experimental, is still not the treatment of choice.

Principles of Treatment

Contraindications

Before beginning to evaluate a patient for lithium therapy, one must consider in which patients it cannot be used. There are no absolute contraindications for its use and no allergies to the drug exist. Certainly, however, one would not give lithium to a patient in dire medical condition, as in acute congestive heart failure, just following a myocardial infarction, or during renal or hepatic failure.

Relative contraindications are based upon known facts regarding lithium's physiology and metabolism. Lithium is excreted entirely by the kidneys, hence chronic renal failure forms one relative contraindication. However, numerous reports indicate lithium's safety in marginal renal conditions.[69,70] Patients with severe diabetes should be checked just before initiation of lithium therapy since the drug can increase glucose levels, but generally diabetes mellitus is no contraindication, nor is epilepsy. Conceivably, as lithium slightly decreases thyroid function, care must be taken in administering the drug to those with hypothyroidism. In practice any lithium-induced hypothyroidism can easily be treated with additional thyroid medication. Lithium in the first trimester of pregnancy may produce a higher incidence of cardiovascular malformations in fetuses, an observation supported by animal research.[71,72] (Table 2 lists guidelines for the use of lithium in women of childbearing age or who are pregnant.) Lithium is safe in the elderly, though, as with most drugs, its dose can be considerably reduced in this population.

In summary, there are few absolute contraindications to lithium's use except in those patients undergoing serious medical emergencies. Relative contraindications are rare and must be weighed

TABLE 2.—*Guidelines for the Use of Lithium in Women of Childbearing Potential or Who Are Pregnant*

A. Treat only for unequivocal indications
   1. Acute manic episodes.
   2. Prophylaxis of severe and frequent manic attacks.
   3. Prophylaxis of severe and frequent depressive attacks if lithium has been shown to prevent such attacks in the past.

B. Urge women taking lithium to avoid pregnancy.

C. Withdraw lithium in the first trimester unless acutely indicated, as under A 1, 2, 3.

D. Adjust dose to lowest effective level.

E. Measure serum lithium levels monthly to achieve lowest possible dosage levels.

F. Avoid fluctuations of serum levels which might be transmitted to the fetus as "pulses" of lithium.
   1. Keep sodium intake constant. Beware of:
      a. Use of diuretics.
      b. Use of a low sodium diet.
      c. Use of a weight reduction diet.
      d. Vomiting.
      e. Excessive perspiration.
   2. Use three times daily dose or, if available, sustained-release tablets. Avoid large single or double daily doses.

TABLE 3.—*Evaluation Before Lithium Therapy*

Complete physical examination.
Complete blood count.
Urinalysis, including protein and formed elements.
Sedimentation rate.
Blood urea nitrogen or creatinine.
Electrocardiogram.
Triiodothyronine (T_3), thyroxine (T_4) or protein-bound iodine studies.

TABLE 4.—*Commercially Available Lithium in the United States*

Company	*Trade Name*	*Dosage Form*
Roerig	Lithane	300 mg tablets
Rowell	Lithonate	300 mg capsules
Smith, Kline, and French	Eskalith	300 mg capsules

against the risk to the patient's medical condition should he suffer an unchecked manic or depressive episode.

Evaluation Before Lithium Therapy

Lithium produces documented clinical effects on a number of organs; their function must be assessed before the initiation of lithium therapy. Table 3 lists the currently accepted physical and laboratory evaluation before initiating therapy with lithium.[73-75]

Dosage

Lithium carbonate is generally administered under two different conditions: acute attacks of affective illness and interval conditions before or following an acute attack. For acute disorders, such as an acute manic condition, 600 mg of lithium carbonate is usually prescribed three times per day, a daily dose of 1,800 mg.[76,77] For patients beginning lithium therapy but not undergoing an acute affective attack, or for patients now in remission, a maintenance dosage is required. Most authors have advised 300 mg of lithium carbonate three times per day.[78] Blachly has commented favorably on the advisability of lower dosages and serum levels, especially for the protective maintenance of patients repeatedly suffering endogenous depressions.[79] Many clinicians have pointed out the narrow range within which lithium is safe.

Patients to whom lithium is being given prophylactically may experience the beginnings of a manic or depressive attack; usually such an episode will be highly modified by the presence of lithium. To fully counter such an attack the lithium dosage is usually increased to the level originally required to control earlier acute symptoms. By identifying these signs of incipient illness in a patient it is possible almost totally to eliminate recurrent affective episodes.[80]

TABLE 5.—*Guidelines for the Determination of Serum Lithium Levels*

Weekly during the first month of treatment.
Monthly for the next two months.
Every three to six months thereafter.
One week after any increase or decrease of dose.
Weekly during other illness, such as influenza.
Monthly during pregnancy.
The day after parturition.
Immediately upon exacerbation of an affective episode.
More frequently during the use of special diets.

The vast majority of investigators report prescribing lithium carbonate in divided doses three times per day. Our own observations support those of Schou, who recommends twice daily dosages except for severely ill patients.

Table 4 shows the forms of commercial lithium available in the United States today.[81-84]

Serum Levels

The ability to accurately determine levels of lithium in patients' sera has contributed significantly to the safety and efficacy of its use. No other psychotropic agent can be so reliably assessed and for the first time psychiatric researchers can easily correlate serum levels of the drug with observable behavioral changes.

Most authorities recommend obtaining the first serum level seven days after initiating therapy with lithium because it takes this long to reach homeostasis. Thereafter levels should be obtained once per week for the first month, then monthly for the next two months, then every three to six months thereafter.

Table 5 lists reasons for more frequent lithium level determinations. Generally, any shift towards lower sodium levels (increased diaphoresis, vomiting, diarrhea, diuretics, diets) will increase lithium levels. In those with chronic illnesses or the elderly the level might also be checked more frequently.

Most authors agree that therapeutic serum levels are between 0.5 and 1.6 mEq per liter. For longer term maintenance therapy levels between 0.5 and 1.2 mEq per liter are appropriate. Lithium levels exceeding 2.0 mEq per liter should dictate a lowering of dosage as toxicity at these levels may be imminent. However, the correla-

tion between clinical signs of toxicity and serum lithium levels is occasionally mysteriously low.[85-87]

Toxicity

Early Side Effects

Reports of lithium's ill effects upon the body have appeared since the beginning of its use in medicine.[88-108] Such reports often reflect either the intake of very much larger quantities than are presently advised or the unrestricted and uncontrolled use of lithium salts as substitutes for sodium chloride. Table 6 lists the most common side effects associated with lithium therapy in psychiatry today in order of approximate appearance and frequency. Table 7 outlines several conditions that increase the risk of escalating lithium levels, given a constant dosage. Most clinicians are aware that once taking lithium the patient should not engage in a low sodium diet or use diuretics. Both maneuvers deplete bodily reserves of sodium, thereby greatly increasing the possibility of lithium toxicity. Care must be taken in the treatment of those with cardiovascular heart disease, hypertension and pregnancy, as these patients may require low sodium diets or diuretics.

Mode of Action

How can such a simple ion as lithium effect such drastic changes in mood? There are two main hypotheses attempting to explain lithium's effects. The monoamine hypothesis of affective disorders poses that deficiencies in central monoamines, chiefly norepinephrine, can cause depression and that excesses of such monoamines cause mania. In fact this is, of course, too simply put. Monoamine theorists are now explaining the dynamic relationships between and among the various amines, chiefly norepinephrine, serotonin and dopamine, and their metabolites. There is exciting new research that promises to predict, from a study of brain amine metabolites, not only in what diagnostic category a patient belongs, but to what drug he will best respond.

Studies show that lithium significantly facilitates norepinephrine uptake by presynaptic neurons, thereby enhancing its destruction.[109-111] Other research shows that lithium exerts a stabilizing effect upon those enzymes involved in the degradation of the monoamines.[112,113] Recent investigation points to effects on several central nervous system enzyme systems, including those involving cycloadenosine monophosphate, an

TABLE 7.—*Conditions Which Increase the Risk of Escalating Lithium Levels*

- Diminished bodily sodium reserves.
  - Low sodium diet.
  - Other "special" diets which, by their nature, lower sodium intake, e.g., weight reduction diets.
  - Bouts of vomiting.
  - Bouts of diarrhea.
  - Excessive perspiration.
  - Use of diuretics.
- Acute renal disease.
- Infections.
- Pregnancy and delivery.
- Remission of an acute manic attack.

TABLE 6.—*Common Side Effects of Lithium—Listed in Approximate Order of Appearance and Frequency*

Gastrointestinal System
- Nausea
- Thirst or dry mouth
- Anorexia or metallic taste
- Vomiting
- Diarrhea

Neuromuscular System
- Tremor
- Weakness
- Blurry vision
- Ataxia
- Fasciculations
- Hyperactive reflexes
- Clonus
- Chorea-athetosis

Cardiovascular System
- Pulse irregularities
- Hypotension
- Circulatory collapse

Central Nervous System
- Lethargy/Drowsiness
- Dizziness
- Mental dullness/Trouble concentrating
- Slurred speech
- Sensory loss
- Incontinence
- Confusion
- Restlessness
- Delirium
- Convulsions
- Stupor
- Coma

Renal System
- Polyuria
- Edema
- Dehydration
- Acute renal failure

Miscellaneous
- Aggravation of acne and other dermatologic conditions
- Weight gain

enzyme thought to be involved with the function of norepinephrine and in the "switch" process from depression into mania.[114,115] The discovery of lithium as a psychotropic drug has created intense interest in the biochemistry of affective disorders and significantly improved our ability to treat patients with these disorders.[116-125] Another overriding value of lithium, in addition to its use in clinical psychiatry, may be derived from the knowledge it can provide about the mysteries of man's moods.

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Specialty Conference

Participants

PIERRE M. DREYFUS, MD
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ERNEST D. GARDNER, MD†
JAMES S. LIEBERMAN, MD
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Refer to: Dreyfus PM, Oshtory M, Gardner ED, et al: Cerebellar ataxia: Anatomical, physiological and clinical implications—University of California, Davis, School of Medicine, and Sacramento Medical Center (Specialty Conference). West J Med 128:499-511, Jun 1978

Cerebellar Ataxia

Anatomical, Physiological and Clinical Implications

PIERRE M. DREYFUS, MD:* *Ataxia, or the inability to coordinate voluntary movements, constitutes a dramatic and important neurological symptom that is usually indicative of structural disease of the nervous system. Ataxia can result from lesions in a variety of different anatomical sites: peripheral nerves, spinal cord, brain stem, cerebellum, and frontal or parietal lobes. Ataxia also occurs in diseases affecting the labyrinth of inner ear and it may be caused by drugs and toxic substances. Finally, ataxia may be of psychiatric origin—hysteria or malingering.*

The diagnosis of ataxia is best determined by clinical maneuvers that show either the inability to dissociate movements requiring skill and speed (dyssynergia) or to gauge speed, distance or power of a movement (dysmetria), or a disturbance of the function of reciprocally innervated muscle groups with diametrically opposed function (dysdiadochokinesia). In addition, alterations in tone (hypotonia) and reflex activity (hyporeflexia) or pendular reflex activity, and abnormal movements, such as intention, action or resting tremor, can sometimes be shown.

In this specialty conference, the topic of ataxia caused by dysfunction of the cerebellum or its connections will be discussed. An attempt will be made to review briefly some basic aspects of cerebellar anatomy and physiology and to discuss some of the common neurological disorders of adults and children in which cerebellar ataxia is a prominent feature. These diseases are, for the most part, not treatable. However, a few are amenable to treatment that results in definite improvement, and some are completely reversible.

Dr. Oshtory will now present the case of a patient whose chief complaint was that of progressive ataxia.

Case Presentation

MEHERJI OSHTORY, MD:‡ A 45-year-old alcoholic white man presented to the Sacramento Medical Center because of progressive unsteadiness of gait.

One year before admission, the patient began having difficulty with balance. He stumbled and fell frequently when confronted with obstacles in his path and he often reached for support to maintain balance. His neurological deficit progressed steadily to the point that he walked with his feet far apart, held onto objects and had great difficulty in turning. The patient became aware of an increased tendency to sway and had fallen frequently during the months before admission to hospital.

*Professor and Chairman, Department of Neurology, University of California, Davis, School of Medicine.

†Deceased.

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He said that weakness, loss of consciousness, headache, visual disturbance, vertigo, tinnitus, weight loss and anorexia had not been problems.

Neither the patient's medical history nor his family medical history included any relevant material. The patient lived in a boarding home and his drinking habits varied according to his financial status. His average alcohol consumption had varied from a fifth (one fifth of a gallon) to a quart of alcohol (whiskey or gin) per day for some years. His nutritional intake was marginal, depending largely on his appetite, alcohol consumption and financial reserves.

When admitted to hospital the patient was seen to be undernourished and had a small bruise on the left forehead, incurred during a recent fall. Vital signs were normal. Examination of the chest, heart, abdomen, genitalia and rectum showed no abnormalities.

On neurological examination the patient was cooperative and oriented in all spheres. The cranial nerves were normal except for mild horizontal and vertical nystagmus, most pronounced on left lateral gaze.

The patient was unable to stand upright and still with his feet together; he assumed a broadened base and there was a moderate degree of truncal ataxia. His gait was extremely ataxic and he had to hold onto furniture or walls near him for support. Executing turns was particularly difficult for him because he tended to fall in the direction of the turn. Power and tone were normal in all extremities and no involuntary movements could be elicited.

Tests for coordination showed a mild intention tremor in both upper extremities. Rapid alternating movements were done normally. The heel to shin test showed moderate impairment bilaterally and dysmetria of rapid foot tapping was noted.

Deep tendon reflexes were normal and symmetrical in the upper extremities. In the lower extremities, knee jerks were present bilaterally and equal, but the right ankle jerk was absent and the left ankle jerk was notably diminished. Abdominal and cremasteric reflexes were intact bilaterally. Plantar responses were flexor.

On sensory examination there was mild impairment of vibratory sense over both ankles and toes; other modalities were intact.

Laboratory examinations showed a hematocrit of 38.9 percent and hemoglobin value of 13.3 grams per dl. Mean corpuscular volume was 107 and the blood smear showed macrocytosis and variation in size and shape of red cells. Total leukocyte count, sedimentation rate, electrolytes and levels of serum protein, hepatic enzymes, serum vitamin B_{12} and folic acid were all within normal limits. X-ray studies of the chest and the skull showed no abnormalities. EEG, brain scan, and spinal fluid examinations were normal.

Comments

Because of the insidious onset of truncal ataxia in the absence of demonstrable systemic disease,

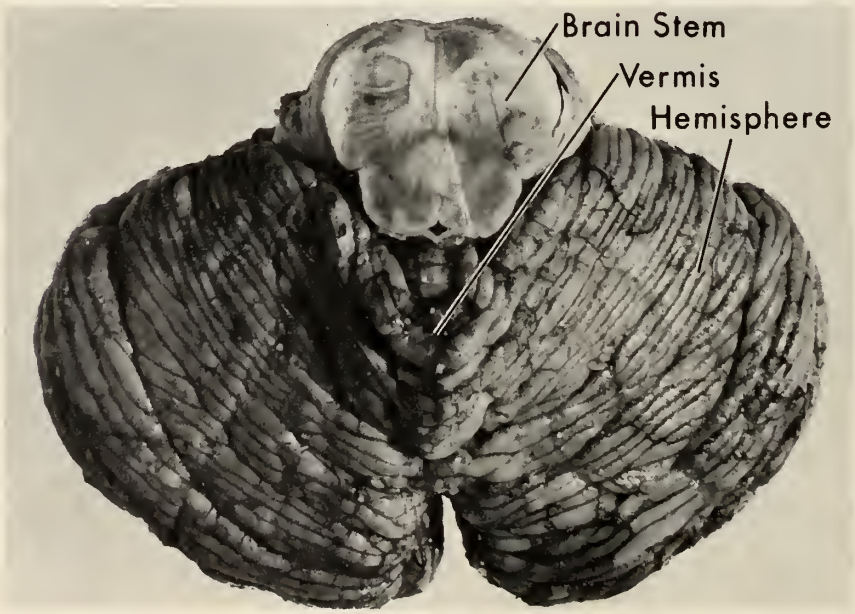

Figure 1. — Superior view of the cerebellar hemispheres. (Courtesy of Drs. G. York and W. Ellis.)

the diagnosis of cerebellar degeneration associated with chronic alcoholism was entertained.

DR. DREYFUS: *Thank you, Dr. Oshtory. I have asked Dr. Gardner to discuss briefly the applied anatomy of cerebellar ataxia.*

Applied Anatomy of Cerebellar Ataxia

ERNEST D. GARDNER, MD:* The human cerebellum lies in the posterior fossa, in an infratentorial position. It is connected to the brain stem by three pairs of peduncles and is grossly divisible into two hemispheres and a median portion termed the vermis (Figures 1-3). The cerebellum receives its arterial supply from the vertebral-basilar system. It is important to emphasize the infratentorial position of the cerebellum, and its relationships to the tentorial notch above, the foramen magnum below, and the fourth ventricle and brain stem in front. Expanding lesions of the cerebellum may result in herniation upward or downward, and may compromise the ventricle, the circulation of cerebrospinal fluid, and the brain stem and its cranial nerves.[1]

The hemispheres and vermis of the cerebellum are deeply partitioned into folia and lobules that have a complex terminology (often based upon comparative neuroanatomy) that need not concern us here. What should be emphasized is that

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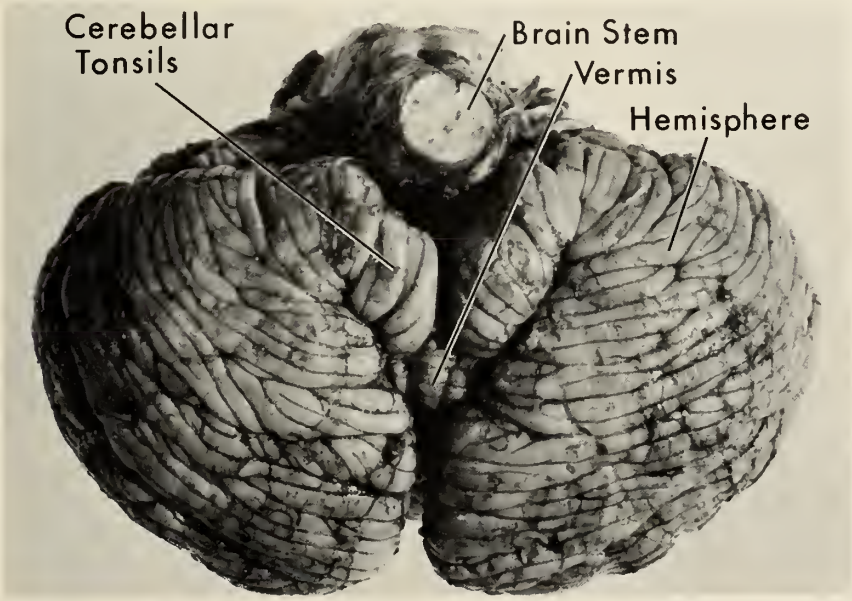

Figure 2.—Inferior view of the cerebellar hemispheres. (Courtesy of Drs. G. York and W. Ellis.)

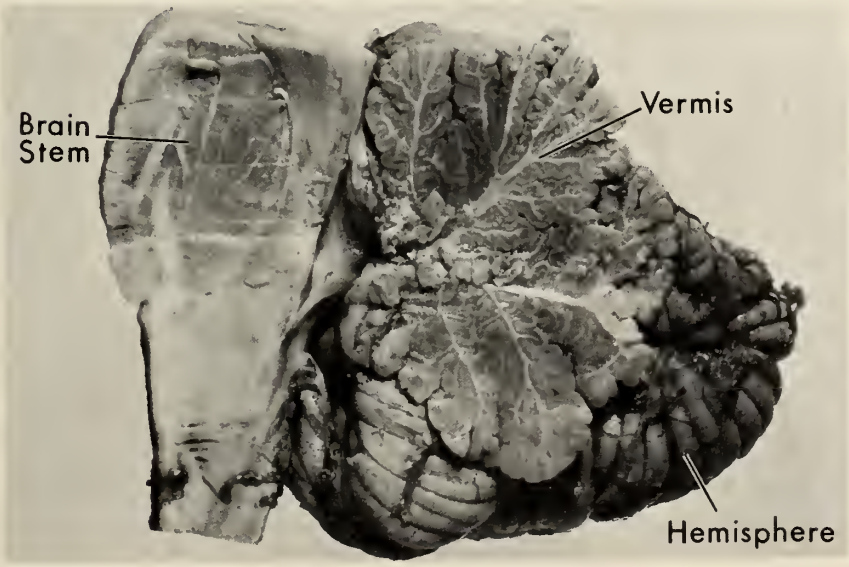

Figure 3.—Sagittal view of the cerebellar hemispheres showing the vermis. (Courtesy of Drs. G. York and W. Ellis.)

the cerebellum—in common with the cerebrum—has a surface layer of gray matter, but that—in contrast to the cerebrum—its cortex is of uniform thickness and synaptic arrangement.[2] Leaving aside the details of cortical structure, it can be stated that the cortical output is by way of the axons of Purkinje cells. These axons for the most part project to the intracerebellar (deep) nuclei, which are masses of gray matter contained within the white matter that forms the interior of the cerebellum. Axons from nerve cells in these nuclei, in turn, leave the cerebellum and comprise the cerebellar output.

In order to carry out its functions, the cerebellum requires information about the position of the body, angles and torsion at joints, tension in muscles and tendons, frequency of muscular contraction, states of autonomic functions, stimulation of skin and subcutaneous tissues and special sense organs, and activity in cerebral cortex and basal ganglia.[3] Signs of cerebellar dysfunction, including ataxia, may arise if information does not reach the cerebellum, if the cerebellum itself is involved or if the cerebellar output is interrupted. In addition, some circuits of the cerebellum appear to be preset—that is, genetically determined—and when activated (perhaps by signals from the cerebral cortex) may bring about a pattern of movement before receiving any information from peripheral receptors.

It is a matter of clinical importance that the control mediated by the cerebellum is largely ipsilateral—for example, the right cerebellar hemisphere is related to the right half of the body. It may be that this relationship is even more precise, that a specific area of a cerebellar subdivision may have input-output connections with a specific part of the body, such as a limb. However, concrete evidence for this specificity in humans is still lacking.

Cerebellar Input and Output

Nerve impulses that comprise the cerebellar input reach the cerebellar cortex by way of pathways that enter the cerebellum over its peduncles. Whatever the pathway, the constituent fibers are usually well myelinated and rapidly conducting. The impulses that comprise the output leave, for the most part, from the deep cerebellar nuclei by way of or adjacent to the peduncles. The input-output arrangements can also be termed loops, the general principles of which are briefly outlined below (Figure 4).

Vestibular Loop

Impulses initiated by the stimulation of receptors in the vestibule and semicircular canals—that is, by the position of the head and by linear and rotational movements of the head—reach a small portion of the inferior cerebellum termed the flocculonodular lobe (also called the archicerebellum). The output is to those vestibular, reticular and motor nuclei of the brain stem that are concerned with the control movements of the eyes, head, neck and upper trunk.[1]

Disorders of this loop resemble vestibular disorders. Moreover, this part of the cerebellum is the common site of origin of medulloblastomas.

Spinal Loop

Impulses initiated by the stimulation of receptors in skin, muscles, tendons and joints (especially of the limbs) reach the cerebellum first by a number of ascending spinal pathways (and certain brain stem pathways) and then by way of the inferior and superior cerebellar peduncles. The portion of the cerebellum to which these impulses are chiefly directed is the vermis, sometimes termed the paleocerebellum. The output is from certain of the deep cerebellar nuclei by way of the inferior peduncle and is directed to those vestibular and reticular nuclei of the brain stem that are especially concerned with the control of limb musculature.[1]

It is important to emphasize that the multiplicity of spinal pathways provides a wide margin of safety. Consequently, ataxia from spinal lesions can be temporary unless there is widespread specific involvement of these paths.

Neocortical Loop

The cerebellar hemispheres (sometimes termed the neocerebellum), which are as prominent in humans as are the cerebral hemispheres and cortex, receives a massive input from the neocortex of each cerebral hemisphere. The impulses are carried by fibers that descend in the internal capsules and cerebral peduncles to the pons, where they are relayed to the cerebellum by axons that form the middle cerebellar peduncles.[1]

The output of the neocerebellum is chiefly from the dentate nuclei (or the deep nuclei), whose axons form most of the superior cerebellar peduncles. The axons of a given superior peduncle cross in the midbrain, where some end in the red nucleus. Others continue to the thalamus (to the same nuclear region that relays impulses

from certain basal ganglia) and thence back to the cerebral cortex, especially the motor cortex. The projection to the thalamus is sometimes known as the dentato(rubro)thalamic path.[1]

It is evident that the neocerebellum, which comprises the bulk of the cerebellum, forms two extensive contralateral loops with the cerebral cortex, including the thalamus, and that it also has significant descending connections.[4] Signs of cerebellar dysfunction, including ataxia, can result from involvement not only of the cerebellar hemispheres but also of the input-output portions of the loops. However, as in the case of the spinal loop, the multiplicity of connections and their widespread nature often provide a wide margin of safety.

Other Relationships

It is of some interest to note that the cerebellum receives a significant input from the visual and auditory systems by way of tectocerebellar fibers. Also the cerebellum has significant connections with the autonomic centers of the brain stem. The precise nature and functions of these additional relationships are still uncertain.

This brief outline of cerebellar anatomy is intended to serve as a basis for the physiological and clinical discussions that follow.

DR. DREYFUS: *Thank you, Dr. Gardner, for a most lucid discussion. Dr. Lieberman will now review briefly the practical aspects of cerebellar physiology.*

Practical Aspects of Cerebellar Physiology

JAMES S. LIEBERMAN, MD:* Recent studies concerning cerebellar physiology have been focused upon either the basic information-processing properties of the organ or the relationship of cerebellar function to clinical dysfunction.[4-6,9]

It is now quite clear that the cerebellum is a very complex neural organ that functions basically as an error-detecting and error-correcting computer concerned with the smooth control of movement.[4,5] In addition it plays an important role in the maintenance of muscle tone and, in fact, may also play a role in the initiation of certain movements.

As detailed in the section on applied neuroanatomy, the cerebellum consists of a cortex and

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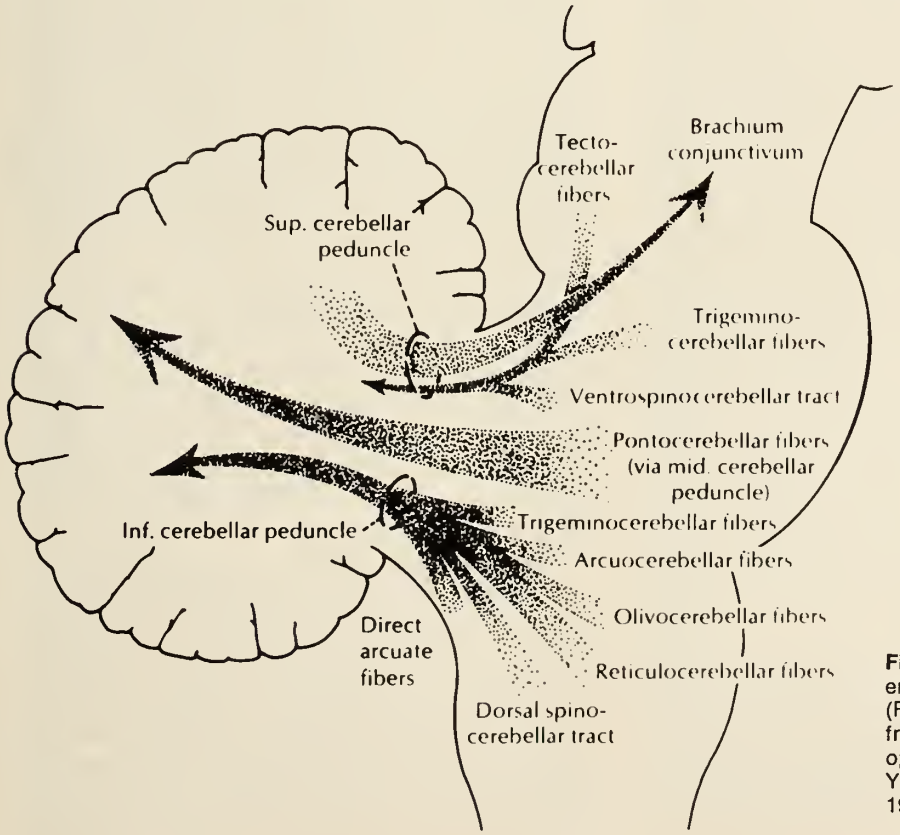

Figure 4.—Afferent and efferent cerebellar connections. (Reproduced with permission from Matzke and Foltz: Synopsis of Neuroanatomy. New York, Oxford University Press, 1967.)

a system of deep cerebellar nuclei. All of the neurons of both the cerebellar cortex and nuclei are in a state of continuous activity, with a resting firing rate of 20 to 100 Hz as they await synaptic input signifying the arrival of information from afferent pathways. Therefore, each cell is already "primed" to respond to synaptic input by raising or lowering its firing frequency.[4,5]

Afferent information to the cerebellum is delivered to the cerebellar cortex by either the climbing fiber system via the olivary nuclei or from all other afferent paths via the mossy fiber system. Experiments show that stimulation of mossy fibers excites granule cells and their axons, the parallel fibers; this in turn leads to excitation of Golgi cells, basket cells, superficial stellate cells and, finally, Purkinje cells. Within the subcircuitry both excitatory and inhibitory pathways exist, but the net effect of the system is felt to be inhibition of cerebellar nuclear cell discharge. The climbing fiber pathway, having arisen from inferior olivary cells, provides monosynaptic excitatory connections with Purkinje cells, and also provides connections with Golgi cells and interneurons via a system of collaterals. Again, the net result of climbing fiber stimulation is inhibition of cerebellar nuclear cell discharge. It is now known that all input to the cerebellar cortex by whatever pathway becomes inhibitory within at most two synaptic relays. Therefore, the entire output of the cerebellar cortex is via Purkinje cell discharges that provide an inhibitory sculpturing of nuclear cell discharges.[4,5]

The cerebellar efferent system consists of projections from the cortical Purkinje cells to the lateral vestibular nuclei, and to the deep cerebellar nuclei. In contrast to the inhibitory effects of cerebellar cortical output, cerebellar nuclear output is basically excitatory with respect to motor function. For example, it has now been concluded that the neocerebellum mediates a tonic facilitatory effect on the dentato-rubro-thalamo-cortical pathway.[6-9] As a result, it can be concluded that, except for direct vestibular connections, the net output of the cerebellum is facilitatory via the nuclear system, as modified by an inhibitory cerebellar cortical system.

Studies primarily concerned with basic information-processing properties of the cerebellum have not always been directed toward an explanation of clinical cerebellar dysfunction. However, several recent studies have provided much information with regard to the pathophysiology of cerebellar signs. These signs in experimental animals were described in the late 19th century, and the Croonian Lectures by Holmes in 1922[10] are regarded as the definitive description of cerebellar disease in man. It is interesting to note that Holmes felt that hypotonia was the most consistent abnormality present and that other important clinical signs, such as dysmetria or tremor, could be due to hypotonia.

Showing the function of the gamma efferent-muscle spindle afferent system and the relationship of the cerebellum to this system has provided the basis for much of the recent research into the physiological basis of cerebellar hypotonia. It has now been clearly shown that (1) a depression of fusimotor efferent and spindle afferent activity results from cerebellar ablation, (2) this depression can be correlated with clinically observable decreased muscle tone (hypotonia) and (3) in an animal with a chronic cerebellar ablation, fusimotor efferent or spindle afferent activity (or both) recovers as hypotonia disappears.[6]

The pathways by which the cerebellum facilitates fusimotor activity have been studied in detail. The anatomic pathways are now well described. Present information suggests that both the fastigio-bulbar pathway and the dentato-rubro-thalamic pathway are involved in the mechanisms of hypotonia. The contribution of each pathway varies from species to species. In lower mammals the fastigial pathway is probably more important while the dentato-rubro-thalamic (neocerebellar) pathway is more important in primates.

Many experiments have been designed to strengthen the theory that hypotonia is a result of diminished neocerebellar facilitation of fusimotor activity. Section of the superior cerebellar peduncles, lesions of the ventrolateral nucleus of the thalamus, ablations of motor cortex and section of the medullary pyramid have all been shown to lead to decreased muscle spindle responses.[6-9]

While the mechanism of cerebellar hypotonia is relatively well understood, the mechanism of other cerebellar signs, including tremor, is poorly worked out. Currently available information would seem to indicate that cerebellar tremor is related to the mechanism of movements projected into the environment, and that the thalamus and areas 4 and 6a of the cerebral cortex may be important in its genesis. Some recent experiments

have suggested the presence of tremor generators within the central nervous system. Both a thalamo-cortical system and an olivo-cerebellar system for generating tremor have been described.[11] It is felt by some investigators that a relative imbalance between the two systems might be the cause of either the intention tremor of cerebellar disease or the resting tremor of basal ganglia disease.

The cause of the ataxia or dysmetria seen in cerebellar disease has been the subject of much recent investigation. The analogy of the cerebellum as an error-detecting and error-correcting computer consisting of several servo loops has led to analysis of dysmetria by both physiologists and servo engineers. It is now becoming evident that lesions in cerebellar pathways (input pathways, output pathways or cerebellum proper) lead to interruption of feedback loops. This feedback loop interruption then results in excessive "oscillation" within the system, producing an instability in the final product—movement.[5] This instability of movement is observed clinically as dysmetria, dyssynergia, dysdiadochokinesia and, perhaps, tremor.

DR. DREYFUS: *Thank you, Dr. Lieberman. Next, I wish to discuss neurological diseases characterized by ataxia that have their onset in adulthood.*

Cerebellar Ataxia in the Adult

Classification of the cerebellar ataxias of adulthood tends to be extremely arbitrary. It seems most appropriate to divide these diseases into three categories: (1) acute, (2) subacute and (3) chronic (see Table 1).

The most common subacute form is the cerebellar ataxia associated with chronic alcoholism, although this disease may present in an acute form. The fact that persistent cerebellar dysfunction can result from chronic, abusive ingestion of alcohol was not generally accepted until 1959, when Victor and his colleagues presented a detailed account of cerebellar degeneration in 50 patients. The clinical and pathological manifestations of the disease are remarkably stereotyped. The syndrome is characterized by a wide-based stance and gait, varying degrees of instability of the trunk and ataxic movements of the limbs. The legs are invariably involved to a greater extent than are the arms, which may be completely spared. Hypotonia of the limbs, nystagmus and dysarthria are relatively infrequent findings.[12]

TABLE 1.—*Cerebellar Ataxia in Adults*

Acute
Intoxications
Alcohol, barbiturates, phenytoin and other anticonvulsants, heavy metals (lead and mercury)
Tumors
Primary, metastatic
Viral infection
Hyperpyrexia
Vascular accidents: hemorrhage and infarction
Demyelinating diseases
Subacute
Alcoholic cerebellar degeneration
Carcinomatous cerebellar degeneration
Chronic
Heredofamilial
Olivo-pontocerebellar atrophy
Parenchymatous cerebellar degeneration
Myxedema
Associated with multiple vascular lesions (von Hippel-Lindau)

In most cases the ataxic syndrome has an abrupt onset, manifesting itself rapidly over a period of several weeks; it then may remain unchanged for many years. However, in some instances, the syndrome evolves slowly over many months. Occasionally symptoms are aggravated by superimposed infection or a bout of delirium tremens.

The pathological changes are restricted to the anterior and superior aspects of the cerebellar vermis, where the major changes consist of degeneration of all of the neurocellular elements of the cerebellar cortex, the Purkinje cells being particularly affected. In advanced cases the anterior parts of the cerebellar hemisphere, the olivary and vestibular nuclei in the brain stem, and some of the so-called roof nuclei of the cerebellum are involved.[12]

In most instances the patient's condition stabilizes or improves upon cessation of drinking and institution of improved nutrition and vitamin supplementation.

Occasionally an acute ataxia in conjunction with Wernicke disease develops in patients. The cerebellar changes in these cases are indistinguishable from those seen in patients suffering from alcoholic cerebellar degeneration who do not have Wernicke disease.[13]

Although the cause of alcoholic cerebellar degeneration remains essentially unknown, there is good evidence that the syndrome is engendered by malnutrition. However, a toxic reaction of

Purkinje cells to metabolites of alcohol, such as acetaldehyde, has not been excluded as a causative factor.

Alcoholic cerebellar degeneration must be distinguished from the cerebellar degeneration caused by the remote effects of carcinomatosis.[12,14]

Remote Effects of Carcinoma

While it is well known that subacute cerebellar degeneration can be caused by the remote effects of carcinoma, the nature of the relationship between the two conditions remains obscure. A variety of neoplasms has been shown to be associated with cerebellar degeneration, the most common being carcinoma of the lung, breast, ovary and kidney. The syndrome may also occur in association with a variety of lymphomas.[14]

Although this disorder closely resembles the one engendered by alcohol, it is possible, on clinical grounds alone, to distinguish patients who have a cerebellar syndrome secondary to an occult neoplasm from those with chronic alcoholism. Victor,[14] summarizing the clinical and pathological data of 26 cases, found that in almost every instance of cerebellar degeneration associated with neoplasia the patient's arms were affected to an equal or greater extent than were the legs. Nystagmus and dysarthria were present in as many as 80 percent of the cases. In addition, in many of the patients there were symptoms and signs not ordinarily considered cerebellar in nature—such as diplopia, vertigo, spasticity, dysarthria, dementia, static and postural tremors, and sensory abnormalities. Spinal fluid abnormalities were noted in half of the cases, consisting of elevated protein in six cases, an abnormal colloidal gold solution curve in eight and an excessive number of lymphocytes in two.

Pathological examination showed more diffuse involvement of the cerebellum in cases of cerebellar syndrome secondary to an occult neoplasm than in patients with alcoholic cerebellar degeneration. All parts of the cerebellum seemed to be affected in the involved folia. All of the neurocellular elements showed pathological alterations and the net effect was Purkinje cell loss and thinning and narrowing of the granular and molecular layers.

It should be noted that in more than 50 percent of the cases of cerebellar degeneration associated with neoplasia the signs of cerebellar disease preceded the overt appearance of the underlying neoplasm by months and sometimes years.[14]

The pathogenesis of the disorder still is unknown. Malnutrition, alcoholism and a variety of toxins have been incriminated. The disease has been compared to the cerebellar degeneration observed in Kuru, which is known to be caused by a transmissible agent. It has been suggested that alterations in the overall immune response experienced by patients afflicted with neoplasia may be responsible either for the activation of a latent virus or for the invasion of a neurotropic virus.

Neoplasia can affect the cerebellum directly. Most primary tumors of the cerebellum, such as astrocytomas and medulloblastomas, tend to occur in childhood, while the neoplasms that most commonly affect the cerebellum of adults are tumors of the cerebellar pontine angle (acoustic neuroma) and metastatic tumors, predominantly from the lung.

Metastatic tumors of the cerebellum tend to present in either an abrupt or subacute manner. Unilateral and bilateral ataxia, signs of brain stem dysfunction, and early evidence of increased intracranial pressure are the most common clinical manifestations. Occasionally a metastasis in the midline of the cerebellum may present with truncal ataxia. This could be confused with either alcoholic cerebellar degeneration or the remote effects of carcinoma of the cerebellum. The use of computerized axial tomography helps in establishing the correct diagnosis.

Cerebello-pontine angle tumors, slow-growing tumors that emanate from cranial nerves in the vicinity of the cerebellum (8th, 7th, 5th), produce symptoms by compressing the cerebellum and its connections. Frequently these symptoms are preceded by tinnitus, progressive deafness and signs suggestive of involvement of cranial nerves. By the time cerebellar symptoms are clinically evident these tumors have reached a relatively large size. In view of the favorable response to surgical intervention, early diagnosis of these tumors is obviously important.

Disorders With Toxic Causes

A variety of organic compounds and heavy metals is known to affect the cerebellum. The most important of these are phenytoin (Dilantin®), 5-fluorouracil, the insecticide DDT, trichloroethylene, arsenic, mercury and manganese. The toxic effects of these compounds are not necessarily restricted to the cerebellum; other parts of the nervous system, including peripheral

nerves, may be involved. Phenytoin and other anticonvulsant medications are unique in that they seem to affect the cerebellum primarily. While the toxic effects of phenytoin tend to be transient, disappearing when the dose is reduced, irreversible cerebellar damage may ensue. The toxic effects of phenytoin are characterized by nystagmus to lateral gaze, which occurs when the blood drug levels rise above the therapeutic level of 20 mg per ml; with levels above 30 mg per ml, dysarthria and ataxia of gait and limbs appear.

Pathological studies in both experimental animals and humans have shown a pronounced loss of Purkinje cells with relative sparing of other cellular elements of the cerebellum following prolonged therapy with phenytoin.[15-17]

Cerebellar Hemorrhage

The diagnosis of cerebellar hemorrhage assumes great importance when we consider that early surgical evacuation of the hematoma is generally followed by good recovery. Unfortunately, diagnosis of this neurological entity is difficult to establish and is often missed. It has been suggested that the diagnosis of cerebellar hemorrhage should be seriously entertained in all patients under 30 years of age who present with the sudden onset of headache followed by evidence of brain stem dysfunction. It should also be considered in patients above the age of 45 suspected of having a subarachnoid hemorrhage. Cerebellar hemorrhage is usually signalled by the sudden onset of severe, occipital, generalized headache. Vomiting follows, then drowsiness, stupor and finally coma. The symptoms progress at varying rates, moving from one to another in a few minutes, or reaching the final coma over a period of a day or so. Signs of brain stem dysfunction—as .evidenced by pinpoint pupils, oculomotor dysfunction, nystagmus, facial nerve palsies and dysarthria—are quite common, while signs of meningeal irritation tend to be rare. While signs of cerebellar dysfunction, such as truncal instability and dysmetria of the limbs, may be present, they are often absent.

The diagnosis of cerebellar hemorrhage can usually be confirmed by computerized axial tomography. Lumbar puncture should be avoided since it can cause tonsillar herniation.

Hypertension is the most common cause of cerebellar hemorrhage, which in turn constitutes 10 percent to 15 percent of all intracranial hemorrhages secondary to hypertension. Less common causes are vascular malformations, aneurysms, hemorrhagic diathesis and hemorrhage within a tumor or infarct.[18,19]

Hyperpyrexia

Hyperpyrexia caused by infection or heat stroke may be responsible for a pure cerebellar syndrome. The acute neurological manifestations of profound hyperthermia tend to be those of coma and generalized convulsions, frequently complicated by shock and renal failure. In patients who survive the initial stages of the illness, signs of widespread cerebral dysfunction may be seen: confusion, pseudobulbar palsy and spastic paraparesis. These abnormalities may resolve gradually, leaving the patient with a profound cerebellar syndrome characterized by dysarthria, dysmetria, and ataxia. A study of 125 fatal cases of heat stroke by Malamud and co-workers has shown that the cerebellum seems to be affected to a greater degree than is any other part of the nervous system. Purkinje cells tend to degenerate in all parts of the cerebellum—that is, in the hemispheres and in the vermis.[20]

Familial Ataxias

The familial ataxias are a group of genetically determined disorders that can be loosely classified according to their age of onset. In adults, two distinct disease entities can be recognized: (1) olivopontocerebellar degeneration and (2) cortical cerebellar degeneration. Olivopontocerebellar degeneration usually begins in the fourth or fifth decade of life with symptoms of unsteadiness of gait that progress to severe truncal ataxia, dysmetria of arms and eventually dysarthria. Bowel and bladder sphincters can be involved; in some cases choreiform movements have been described. Sensation, muscle power and reflex activity are usually intact. As the name implies, the disease process involves the medulla, the pons, and the cerebellum. Although olivopontocerebellar degeneration is, in most instances, genetically determined, sporadic cases have also been described. Cortical cerebellar degeneration has its onset relatively late in life. It is a slowly progressive disease characterized by pure cerebellar symptoms and signs. The disease process is confined to the cerebellar cortex. The fact that this disease rarely occurs in more than one member of a family may be due to a dominant mutant gene with incomplete penetrance. In the absence of a family his-

TABLE 2.—*Cerebellar Ataxia in Children*

Acute
Intoxications with drugs or heavy metals
Encephalitis
Posterior fossa tumors
Head injury
Associated with remote neoplasms: such as neuroblastoma
Chronic
Developmental anomalies
Heredofamilial disorders
Friedreich ataxia
Ataxia with muscle atrophy (Roussy-Levy)
Ataxia with myoclonus (Ramsay-Hunt)
Ataxia telangiectasia (Louis-Bar)
Acanthocytosis (Bassen-Kornzweig)
Lipid storage disorders
Miscellaneous
Hartnup disease
Leigh encephalopathy
Intermittent ataxia and pyruvate decarboxylase deficiency

tory, the diagnosis is very difficult to establish. To date, the cause of the familial cerebellar degenerations remains obscure.

DR. DREYFUS: *I have asked Dr. Vijayan to discuss the ataxias most commonly encountered in children.*

Cerebellar Ataxia of Childhood

NAZHIYATH VIJAYAN, MD:* After reviewing the main causes of the cerebellar ataxias that occur in adults, it seems appropriate to discuss some disorders that are encountered predominantly in children. Since time does not permit a complete and detailed discussion of all of the neurological syndromes associated with ataxia, Table 2 provides a list of the most common diseases.

In discussing the acute ataxias of childhood, it is important to keep in mind the entity known as acute cerebellitis (acute cerebellar ataxia),[21] a self-limited disorder characterized by the sudden onset of ataxia, dysmetria and nystagmus, and frequently preceded by a nonspecific upper respiratory infection, headache, vomiting, and, on occasion, drowsiness of brief duration. Fever and nuchal rigidity are usually absent. Examination of the cerebrospinal fluid may show the presence of a few lymphocytes and slight elevation of the protein content; findings on an electroencephalogram may be mildly abnormal in approximately half of the patients examined. A viral cause has been postulated, although the infectious agent has rarely been identified. Several different viruses have been incriminated, including varicella, Echo type 9, coxsackie B, poliomyelitis, measles, mumps and rubella. Of these, varicella has been the one most commonly identified. In the course of viral illnesses with exanthematous manifestations, the rash usually precedes the advent of ataxia; on very rare occasions the sequence of events is reversed. Sometimes signs of brain stem dysfunction—such as cranial nerve palsies, disturbed ocular motility and extensor plantar responses—can be elicited. Acute cerebellitis must be differentiated from a posterior fossa tumor. On occasion this can be accomplished by means of computerized axial tomography. More often, however, the clinical course of the illness points to the correct diagnosis. In most cases of acute cerebellitis, recovery begins in a matter of days and is usually complete within a few weeks. Signs of increased intracranial pressure are rarely detected.

Cerebellar Ataxia Associated With Remote Neoplasms

In adults the association of cerebellar degeneration and the remote, nonmetastatic effects of neoplasia is well recognized. A similar syndrome has been described in children who harbor a neuroblastoma. Characteristically these patients present with ataxia of gait, dysmetria of the extremities, dysarthria, and chaotic eye movements referred to as *opsoclonus,* which resembles nystagmus. Since neuroblastoma cells secrete epinephrine, large concentrations of the breakdown product vanillylmandelic acid (VMA) can be detected in the patient's urine. Neuroblastoma is one of the most common types of solid tumors encountered in children and carries the most favorable prognosis. The distressing neurological symptoms improve or disappear altogether following early diagnosis and removal of the tumor. The underlying physiological mechanisms by which the neoplasm affects cerebellar function remains unknown.[22]

Having discussed two of the important causes of acute ataxia of childhood, let us consider some of the more common chronic forms.

Developmental Anomalies

A number of well-known developmental anomalies of the posterior fossa and the cranio-vertebral junction involve the cerebellum and are responsible for chronic, progressive ataxia. The most common disorders are agenesis of the cerebellum,

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the Dandy-Walker syndrome, and the Arnold-Chiari malformation. *Agenesis of the cerebellum* produces mild ataxia, which lessens with age by virtue of compensatory mechanisms.[23] The *Dandy-Walker syndrome,* a congenital anomaly caused by occlusion of the foramina of the fourth ventricle, leads to dilatation of the fourth ventricle and impairment of cerebellar function. The condition is characterized by a bulging occiput, progressive ataxia, nystagmus, and cranial nerve deficits.[24]

The *Arnold-Chiari malformation,* in which the cerebellum is elongated and the cerebellar tonsils protrude through the foramen magnum into the cervical spinal canal, is commonly associated with such other major anomalies as myelomeningocele, and cerebral and ventricular abnormalities. Although cerebellar ataxia is one of the major symptoms, lower cranial nerve palsies, spinal cord involvement and hydrocephalus are common manifestations. Since the progressive neurological deficit can be retarded by surgical procedures, appropriate diagnostic tests, including air or contrast myelography, should be seriously considered.[23,24]

Hereditary Disorders

A number of hereditary disorders that are characterized chiefly by ataxia are encountered in childhood. The best described are Friedreich ataxia, ataxia telangiectasis, ataxia with myoclonic epilepsy, ataxia associated with abetalipoproteinemia and acanthocytosis, and ataxia associated with a metabolic defect.

Only the most common and well-defined entities will be considered here.

Friedreich ataxia is one of the most common forms of hereditary spinocerebellar ataxias, usually inherited in an autosomal recessive manner. Over half of the cases have their onset before the age of 10 and in most of the cases symptoms develop before the person involved reaches the age of 25. Afflicted members of a family tend to experience the first symptoms of this disease at the same age, but the rate of progression varies considerably from person to person.

The earliest symptoms and signs are related to ataxia of gait. Many children are described as being "slow developers" or clumsy long before ataxia is manifest; however, many afflicted persons give a history of normal growth and development before the onset of ataxia. In many instances, a high-arched deformity of the foot is noted at the time of onset of ataxia. Typically, the ataxia is of the cerebellar type characterized by broadbased gait and incoordination of legs. Subsequently ataxia spreads to the upper extremities and dysarthria develops. As the disease progresses, evidence of posterior column dysfunction—loss of joint position sense, vibratory sense and tactile discrimination—becomes prominent. Impaired posterior column function tends to aggravate the patient's ataxia.

During the early phases of the disease, deep tendon reflexes disappear in the legs; eventually they are lost in the upper extremities as well. Extensor plantar responses tend to develop later. Horizontal nystagmus may be seen in more than half of the patients while dementia is a rare and late complication of the disease.

In addition to neurological manifestations, cardiological manifestations may be observed, such as myocarditis, conduction defects and congestive failure. Because of paraspinous muscle weakness, thoracic kyphoscoliosis is a common complication.

As one might expect, the pathological changes are seen in the dorsal columns, the dorsal and ventral spinocerebellar tracts, and pyramidal tracts of the spinal cord. The dorsal roots are also involved. The underlying metabolic defect that is responsible for the extensive degenerative changes is presently under intense investigation. Abnormalities in pyruvic and oxoglutaric acid metabolism may account for some cases of Friedreich ataxia.[25]

Ataxia telangectasia is a genetic disorder, inherited in an autosomal recessive manner. Progressive ataxia becomes apparent as soon as the child begins to walk. Frequently motor development is delayed, to the point where the average patient does not begin to walk before 16 to 20 months of age. Whereas ataxia begins in the lower extremities, it gradually involves the upper extremities and the bulbar musculature. Speech becomes dysarthric and nystagmus is quite common. As the disease progresses, choreoathetosis may develop. The second most characteristic manifestation of the disease is the appearance of telangectasia, usually around the age of 3. These are first seen in the bulbar conjunctiva, the exposed parts of the ear lobes, flexor creases of the upper and lower extremities and, eventually, over other exposed surfaces of the body. As the patient grows older, telangectasia becomes more extensive. The third feature of the disease is the

patient's susceptibility to chronic sinus, ear and pulmonary infections. The latter may lead to bronchiectasis. Despite the fact that neurological disability progresses fairly rapidly, the patient's mentation usually remains intact. Peripheral neuropathy may be seen as part of the clinical picture.

Immunological abnormalities constitute a common finding. Approximately 75 percent of children afflicted with the disease have either absent or reduced levels of IgA. IgM and IgG are most often normal, but IgG may be reduced in some cases. The low IgA levels are thought to be due to reduced rates of synthesis rather than to increased catabolism. Antibody responses to various antigens tend to be poor. The thymus gland of affected children is either underdeveloped or totally absent and peripheral lymphoid tissues show a pronounced depletion of lymphocytes, leading to lymphopenia.

Treatment of this disease is entirely symptomatic. Appropriate antibiotic agents are of value in treating specific infections of the respiratory tract. The administration of gamma globulin has not proven to be very beneficial.[26]

Ataxia Associated with a Metabolic Defect

Ataxia in children may be caused by a number of genetically determined inborn errors of metabolism. While in most cases ataxia presents in a progressive manner, starting relatively early in life depending upon the defect, it also may be present in intermittent bouts of short duration.

Subacute necrotizing encephalopathy, or Leigh disease, is characterized by ataxia, hypotonia, ophthalmoplegia, dysphagia, disturbed vision or hearing, and evidence of peripheral neuropathy. The necrotic lesions found in the brains of children who succumb to Leigh disease, usually in early childhood, are similar in appearance and distribution to those found in the brains of adult patients afflicted with Wernicke disease. An abnormality in pyruvate oxidation appears to be present in most cases. The faulty enzymatic step in this complex biochemical reaction may differ from patient to patient. The administration of thiamine, an essential cofactor in the metabolism of pyruvate, has been found to be effective treatment in some cases. Pyruvate dehydrogenase deficiency, a disease distinguished by progressive or intermittent bouts of ataxia, may represent a clinical variant of Leigh disease. Some cases are known to be thiamine-responsive.[27,28]

Metabolically determined ataxia is quite commonly associated with some degree of mental retardation. Arginino-succinic aciduria, which is caused by an enzymatic block of the urea cycle enzyme (arginino-succinase); Hartnup disease, thought to be the result of an error in the transport of tryptophan and other neutral amino acids in the renal tubules; and abetalipoproteinemia (Bassen-Kornzweig disease), an abnormality of lipid transport, can all cause ataxia of progressive nature.[29]

Most recently a syndrome of unknown cause characterized by short bouts of ataxia, dysarthria and nystagmus lasting one to two hours and dramatically reduced by the administration of acetazolamide has been described in members of two families (Sauer RN, Dreyfus PM: Familial episodic ataxia [personal observations]).

A metabolic screen on the blood and urine should be obtained in patients whose ataxia is not readily explained by a fixed, a progressive or an expanding lesion within the posterior fossa. The urine should be screened for the presence of amino acids, organic acids and catecholamine breakdown products.

A complete description of the long list of diseases that produce ataxia in children would be too extensive to include here.

DR. DREYFUS: *We have attempted to provide an overview of a common neurological disturbance by discussing its anatomy and physiology, and the most important clinical states in which it occurs. It is hoped that, as the basic pathophysiology of some hitherto obscure disorder is elucidated by means of sophisticated immunological, virological and biochemical techniques, the specific causes of some of these diseases will be discovered, leading to effective methods of therapeutic intervention.*

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Smoking and Lung Cancer

IT TAKES A LONG TIME to produce cancer. It may not take nearly so long to stop it—to prevent it. In the early 1950's, when Sir Richard Dahl and Sir Austin Bradford Hill published their information on the relation of smoking and lung cancer, many British physicians, demonstrating considerable intelligence, stopped smoking. In a period of five to eight years after these reports had been published, the rates in physicians had begun to decline, whereas the rates for all adult males in England were increasing. . . . This is an illness in which the effects of personal prevention take place almost immediately upon someone having taken personal preventative action. You stop smoking. Your rates then are the rates of a smoker at the age at which you had stopped. They do not continue to rise. They actually fall initially, and then gradually approach the rates of the nonsmokers. Here's a personal thing that one can do which has an immediate effect. It doesn't seem to matter how long you've smoked—you can take this action yourself, and it works. People say, "Oh, I've smoked 20 years; I guess it doesn't matter any longer." Only if there has been softening of the brain doesn't it matter any longer.

—MARVIN SCHNEIDERMAN, MD, *Bethesda*

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 10, No. 12, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: The ailing health care system—Medical Staff Conference, University of California, San Francisco. West J Med 128:512-526, Jun 1978

The Ailing Health Care System

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. LEE:* *The central issue of this medical staff conference on the ailing health care system is rising costs. Two case presentations illustrating the complex of factors involved in catastrophic medical care costs in a university setting serve as a point of departure for a discussion of the problems surrounding the cost issue from a clinical, ethical and a policy perspective.*

What are some of the facts that have led to this presentation? The costs of medical care are rising rapidly. Expenses for medical care have risen from 4.6 percent of the gross national product in 1950 to 8.6 percent in 1976, when medical care expenditures amounted to $139 billion (Figure 1).[1] *In 1977 it is estimated that these figures will have increased to $160 billion and 8.9 percent of the gross national product. Individual costs have also increased substantially, as have health insurance premiums. Persons who pay out of pocket, those who purchase health insurance, and those who pay the taxes that support government medical care programs all are becoming concerned.*

Hospital care is taking an increasing share of the medical care dollar, even more than professional services and far more than any of the other components of medical care costs. University medical centers and teaching hospitals are accounting for a growing proportion of hospital care expenditures.

An increasing share of federal and state budgets is also being spent for medical care. Federal outlays have risen from $5.2 billion in 1965, the year Medicare and Medicaid were enacted, to $39.9 billion in 1976.[1] *Similarly, the proportion of the federal budget devoted to medical care has risen from 4.4 percent in 1965 to 11.3 percent in 1975. This is one of the reasons politicians are searching for ways to effectively control the rising costs of medical care. The dual problems of rising costs and regulation have become the overriding health policy issues of the 1970's.*

How to control rising medical costs also has become a matter of major concern to deans and other medical educators. Recently, 110 medical school deans issued a statement entitled "America's Health and Medical Costs."† *I would like to quote two passages from that statement: "Be-*

*Philip R. Lee, MD, Professor of Social Medicine, Director, Health Policy Program.

†*America's Health and Medical Costs—A Statement from the Deans of 110 American Schools.* National Fund for Medical Education. Hartford, Conn., 1977. (This statement contained the signatures of all eight California medical school deans, plus the deans of medical schools of the Universities of Oregon and Washington.)

cause of the key role played by doctors in determining many of the costs of care, we believe the nation's health care system can be made cost conscious without compromising the quality of care delivered." We hope that this is the case. The statement also said: "We believe all physicians must become knowledgeable about the fiscal aspects of health policy and sensitive to the economic consequences of their professional decisions." The deans went on in this short report to emphasize the need to provide physicians in training with opportunities to learn more directly about these issues.

The rising individual and national expenditures for medical care have caused such distinguished economists as Victor Fuchs to raise the question, "What are we getting for our money?" Analysts have begun to raise questions about the relationship of medical care to health, the effectiveness of medical procedures and the value of medical care in general. The problem of rising costs is not only leading to more regulation of medical care, but also has given great impetus to the idea that physicians should be at risk in terms of the costs of care generated by their behavior. This is a very old idea. It is strongly embodied in group practice prepayment concepts, and it formed the basis for national policies in the early 1970's to foster the development of health maintenance organizations. One of the newest proposals for national health insurance, designed by Professor Alain Enthoven of Stanford University's School of Business, incorporates this idea; so does the Health Security proposal supported by Senator Edward Kennedy. What would be the implications for faculty and house staff if they were at risk for costs generated by the care provided at university medical centers?

Finally, the problem of the rising costs and catastrophic expenses generated in the care of many sick patients has raised the question of rationing more explicitly than it has been raised in the past. These are some of the issues that we will be discussing this morning. To do so, let us

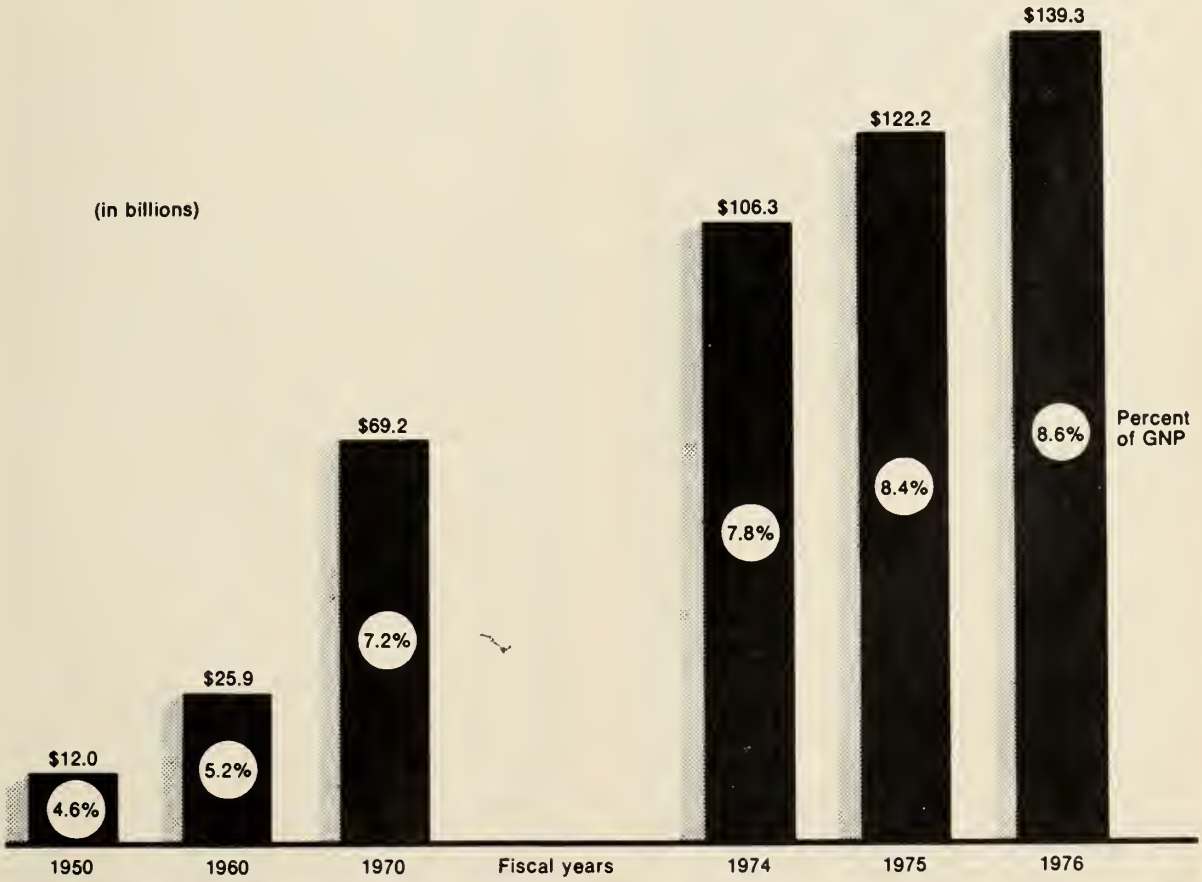

Figure 1.—National health expenditures and percent of gross national product, selected fiscal years 1950-1976. (Reprinted by permission from Gibson and Muller and the Social Security Bulletin[1]).

turn to a case summary of our first patient, which illustrates dramatically how costly, as well as beneficial, medical care can be.

Case Presentation

DR. BRADLEY:* This is the first University of California, San Francisco, (UCSF) admission for this 53-year-old woman who entered with the chief complaint of diarrhea of seven months' duration. Twelve years before admission, the patient had vagotomy and pyloroplasty for recurrent duodenal ulcers with complete relief of symptoms. Three months before admission, she began to have 4 to 20 watery, dark brown stools per day. These were usually postprandial, occassionally nocturnal, and associated with intense lower abdominal pain. Five weeks before admission, the patient was admitted to another hospital with an 11-pound weight loss and hepatomegaly. Findings in the following tests were normal at that hospital: the antinuclear antibody, B_{12}, gastrin, basal acid output, catecholamines, 5-hydroxyindole acetic acid, thyroid function tests, ceruloplasmin, serum immunoglobulins, amylase, stool fat, cortisol, stool ova and parasites × 12, upper gastrointestinal (GI) series with small bowel follow-through, barium enema, sigmoidoscopy, two small bowel biopsy studies, a cholecystogram (using an orally given contrast agent) and a computerized tomography (CT) scan of the abdomen. The following tests gave abnormal findings: elevated liver function tests; slightly elevated eosinophils; mildly low folate; and a carcinoembryonic antigen of 5.0 mg per ml (normal less than 5.0 mg per ml). Selected films from a celiac angiography were said to show a blush in the tail of the pancreas. The patient was given intravenous hyperalimentation, and she was transferred to this hospital.

On physical examination the patient was seen to be thin and in no acute distress; vital signs were within normal limits. The abdomen was nontender with the liver edge palpable two fingerbreadths below the right costal margin. Admission laboratory values included the following: hematocrit of 30.5 percent with normal indices and 2.3 percent reticulocytes; leukocyte count of 7,800 with 4 percent eosinophils; platelet count of 355,000; normal SMA-6, prothrombin time, SMA-12, electrocardiogram (EKG), urinalysis, and chest x-ray.

*William Bradley, MD, first-year medical resident.

The patient's three-month hospital course featured a combination of diagnostic and therapeutic maneuvers. Hyperalimentation was accomplished with a left subclavian line followed by placement of a Broviac catheter, and, finally, a left internal jugular line. When the patient neither ate nor drank, she still had three or four watery stools per day, high in sodium. On a gluten-free, milk-free, low-residue diet, she had 10 to 20 stools per day. Shortly after admission, the celiac angiogram was reviewed extensively and findings were thought to be normal. Upper gastrointestinal series, a barium enema study, colonoscopy and a cholecystogram (with an orally given contrast agent) were all repeated, and again showed no abnormalities. Another biopsy study of the small bowel failed to show Giardia. Results of a biopsy study of the liver were read as nondiagnostic. Sonogram of the pancreas was normal as was another CT scan of the same area. Serum vasoactive intestinal peptide was equivocal at a level of 18 (normal is less than 10). Many antidiarrheal agents were utilized during her hospital stay. Maximal doses of paregoric and Lomotil® (diphenoxylate hydrochloride with atropine sulfate) were found to have a small but beneficial effect. Several therapeutic trials were attempted. Two ten-day courses of tetracycline were given for presumed bacterial overgrowth; metronidazole was given for presumed occult giardiasis; indomethacin was given for presumed prostaglandin-mediated diarrhea secondary to a presumed medullary carcinoma of the thyroid; steroids were given for presumed atypical inflammatory bowel disease. None of these therapeutic trials was found to have a beneficial effect, and it became increasingly obvious that an exploratory laparotomy might be necessary.

During a total hip replacement several years previously, it had been noted that the patient's blood contained an unidentified antibody and could not be cross-matched. Her blood was sent therefore to multiple blood banks, but attempts at cross-matching were all unsuccessful. Crossmatch was then attempted between the patient's three children and five siblings. One brother was compatible. Unfortunately, this brother, who lived in North Dakota, was scheduled for an elective aortic aneurysm repair two days later. This was postponed, and he donated one unit of blood toward his sister's operation. At the last minute, her blood was typed as Vel negative, a rare blood type found in one of 5,000 people;

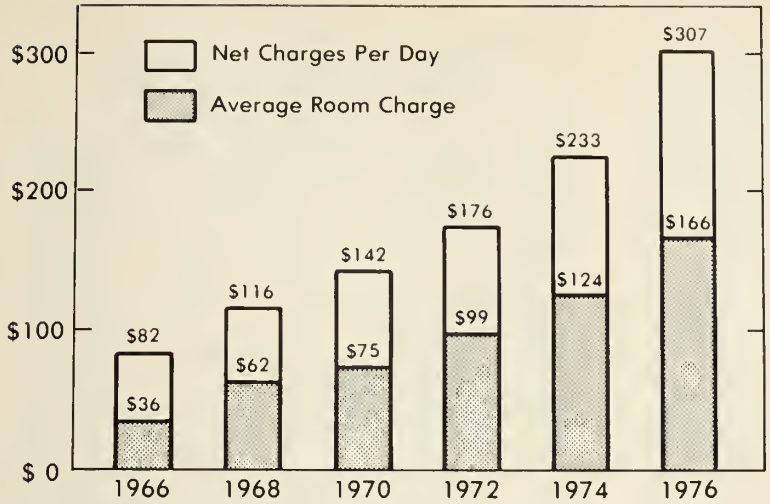

Figure 2.—University of California, San Francisco, Hospital inpatient charges, selected fiscal years, 1966-1976.

three more units were located in the San Francisco Bay area. Exploratory laparotomy was carried out. No obvious masses were found, and 70 percent of the pancreas was resected. The pathology report showed islet cell hyperplasia. She was discharged well three weeks later with only three or four loose stools per day. At follow-up examination the week before this conference, she continued to do well with only two to three bowel movements per day. The final diagnosis was pancreatic cholera; her hospital bill at UCSF was $46,500.

Medical Costs—The Clinical Perspective

DR. SCHROEDER:* I will present preliminary data from a current research project on high cost medical cases, discuss the costs of medical care at teaching hospitals (with emphasis on the use of laboratory and x-ray tests) and examine differences among hospitals and physicians in their use of costly medical services.

The decision of how far to pursue diagnosis and treatment of patients in hospital is one that we all face daily. As hospital costs continue to climb dramatically, questions are being asked about how these decisions are made and what are the cost implications to the patients, to the hospital and to society. Approximately 40 percent of all health care expenditures occur in hospitals. The rise of hospital costs outstrips every other component of medical care. National health expenditures rose 17 percent from 1974 to 1975, 15 percent from 1975 to 1976.[1] Per diem rates at UCSF have climbed proportionately during the past ten years (Figure 2).

*Steven A. Schroeder, MD, Associate Professor of Medicine, Associate Professor of Ambulatory and Community Medicine.

The case just presented shows the degree to which excellent, meticulous medical care in combination with new medical technologies can produce an outstanding patient care outcome. Recently, the newspapers reported the story of a 44-year-old Army mathematician who was admitted to hospital in Washington, D.C., for 270 days. This patient had chronic pancreatitis that was resistant to medical and surgical therapy. His hospital course was even more heroic than that of our patient; prolonged paralysis resulted from administration of curare, given in an attempt to stabilize pancreatic inflammation. The patient finally died after a stormy and complicated course. Two factors made this patient newsworthy: the attempt to treat him with curare, and his hospital bill of $250,000.

How typical are these cases? Are they likely to increase in frequency? Questions such as these have inspired proposals for national catastrophic health insurance that would cover only high cost medical care, such as cases in excess of $5,000 per person per year. A research team at the Health Policy Program, UCSF, is currently working with me to investigate the frequency and the characteristics of hospital patients with high medical expenses in order to judge the need for and the likely impact of a national catastrophic health insurance plan. This study, which is funded by the National Center for Health Services Research and the Henry J. Kaiser Family Foundation, involves 17 acute care hospitals in California's San Francisco and Alameda counties. We define high cost cases as those equal to, or greater than, $4,000 per patient per year. Since $5,000 is commonly discussed as a deductible level for a

TABLE 1.—*Characteristics of Sample of Patients Who Incurred Yearly Charges of $4,000 or More at University of California, San Francisco (UCSF), Hospital and a Community Hospital*

	UCSF Hospital	*Community Hospital*
Number of patients	127	104
Age (years)		
Mean	44.2	67.5
Median	48.5	71.5
Sex		
Men	45.7%	40.4%
Women	54.3%	59.6%
Primary Insurer		
Government (Medicare, Medicaid)	43.7%	73.0%
Nongovernment	56.3%	27.0%
Ethnic Group		
White	82.3%	94.1%
Nonwhite	17.7%	5.9%
Discharge Status		
Alive	90.5%	84.6%
Dead	9.5%	15.4%

national catastrophic health insurance plan, we judge that adding physician charges would bring the average case over the $5,000 level. Our data will probably underestimate patient yearly costs to the degree that it excludes care outside of the hospital, long-term care, psychiatric care, and hospital admissions at other hospitals, such as occurred with this patient. It also excludes inpatient physician and surgeon charges.

So far we have analyzed 12 acute care hospitals in these two counties. The percentage of patients with bills in excess of $4,000 per year in 1976 ranged from a low of 4 percent at one small community hospital to 22 percent at UCSF. The percentage of patients with bills in excess of $10,000 varied from less than 1 percent at another small community hospital to 6 percent at both UCSF and a referral pediatric hospital.

Let us compare the experience at UCSF with a general community hospital in the San Francisco Bay area. UCSF is a large hospital (560 beds) with multiple specialty units; it receives referrals from a wide area. The community hospital is moderate in size (175 beds) and receives referrals from a relatively small area. Annual patient charges at UCSF are about $50 million, as compared with $10 million at the community hospital. Mean patient charges are $3,100 at UCSF and $1,960 at the community hospital.

At UCSF approximately 22 percent of the patient population incurred one-year charges equal to or greater than $4,000. These patients accounted for two thirds of the total charges of $50 million. At the community hospital 10.5 percent of patients had charges equal to or greater than $4,000, accounting for 40 percent of the total hospital charges. The difference between the two hospitals is even greater when $10,000 is used as a cutoff point. Of the cases at UCSF, 6 percent had charges in excess of $10,000, accounting for 34 percent of the total charges; at the community hospital these figures were 2 percent and 4 percent, respectively.

TABLE 2.—*Comparison of Chronicity and Purpose of Admission for Sample of High Cost Patients at University of California, San Francisco (UCSF), Hospital and a Community Hospital (Percentages)*

	UCSF Hospital	*Community Hospital*
Number of Patients	127	104
Chronicity		
Acute	47.2	52.0
Chronic	52.8	48.0
Purpose of Admission		
Palliation	4.7	2.0
Restore to normal function	20.5	13.7
Improve to previously impaired status	40.9	44.1
Diagnostic	33.9	40.2

A more detailed comparison of high cost cases at the two hospitals comes from a sample of 127 patients from UCSF and 104 from the community hospital who were randomly selected from patients with costs over $4,000. As shown in Table 1, patients at the community hospital were much older, suggesting that younger patients are more likely to be referred to a university hospital. The differences in primary insurers reflects the large percentage of community hospital patients covered by Medicare.

In addition to describing routine demographic and clinical data, we made two clinical judgments for each high cost case. First, after a medical record review we divided the cases into acute or chronic, based on duration of illness. Second, we placed each case into one of four categories according to purpose of admission. The two hospitals were not significantly different with respect to chronicity of disease or purpose of admission (Table 2).

Table 3 shows the mean yearly charges by discharge service of the UCSF high cost patients. It is of note that three services had particularly high mean costs: the transplant service, the infant service (which reflects activity in the neonatal

TABLE 3.—*Mean Yearly Charges by Discharge Service of Sample of High Cost Patients at University of California, San Francisco, Hospital*

Discharge Service	*Number*	*Percent*	*Mean Charge*	*Percent Total Charges*
Pediatrics	15	11.8	9,685	13.0
Infants	6	4.7	15,345	8.2
Pediatrics	6	4.7	6,133	3.3
Pediatric surgery	3	2.4	5,467	1.5
Medicine	39	30.8	10,421	36.2
Dermatology	3	2.4	4,910	1.3
Medicine	32	25.2	11,632	33.2
Neurology	4	3.2	4,866	1.7
Surgery	73	57.4	7,828	50.8
Ear, nose and throat	2	1.6	7,674	1.4
Neurological surgery	16	12.6	7,154	10.2
Obstetrics-gynecology	4	3.2	5,235	1.9
Orthopedics	17	13.4	8,010	12.1
Surgery, general	12	9.3	7,343	7.8
Thoracic surgery	7	5.5	7,777	4.8
Transplant	5	3.9	15,574	6.9
Urology	4	3.2	6,721	2.4
Vascular surgery	6	4.7	6,201	3.3
TOTAL	127	100.0	8,844	100.0

intensive care unit) and medicine. Surgical cases constituted almost 60 percent of the high cost cases at UCSF, as compared with about 35 percent at community hospitals.

These data suggest that high cost cases are not only common, but that they account for a large share of hospital charges and revenues, particularly at a university hospital. Comparison of the high cost cases at the two hospitals suggests that selective referral to university hospitals of younger patients and those with surgical conditions is occurring to a substantial degree. Some estimate of the likely growth of high cost cases can be made by noting that 50 percent of all patients had chronic disease (present for more than one year) and that population projections estimate an increasing proportion of elderly persons.

It is not yet clear what outcomes ensue from high cost cases such as these. One report examined outcomes of 226 consecutive critically ill patients who entered the recovery room/acute care unit at Massachusetts General Hospital. Almost 90 percent of these patients were postoperative and required intensive physician and nursing care. In all, 54 percent died within a month, and 73 percent were dead within 12 months of hospital admission. Of the 62 survivors, 27 (12 percent) recovered fully. Hospital charges in 1972-1973 dollars averaged $14,300.[2] In discussing the role of cost considerations in clinical decision making, the authors of this study argue that it is not appropriate to consider withholding care once the patient has been admitted to an intensive care unit. However, they hint at a cost containment strategy whereby admission to intensive care units would be rationed.

Teaching hospitals are special cases in terms of medical costs because of their different referral patterns as well as their educational functions. Attention is now beginning to focus on the extent to which teaching hospital costs are high because of the teaching function. The question appears to be a straightforward one that could be answered by two accounting techniques. First, what proportion of the hospital budget is attributable to house staff salaries and to teaching activities of clinical faculty? And second, to what extent does teaching alter the process of care, for example, by increasing the length of hospital stay or by increasing the use of consultative and diagnostic services such as laboratory and x-ray tests? The question is made a great deal more difficult, however, by the problem of case mix. Most university hospitals care for an unusually large percentage of relatively complicated cases or provide special services such as renal transplantation. Because it has not been possible to control the case mix issue very well, most attempts at measuring teaching hospital costs have not been definitive. Nevertheless, interesting preliminary data are available.

At the University of Rochester, Griner found that laboratory and x-ray tests accounted for 25 percent of the bills of hospital medical patients. During five years at that hospital, costs attributable to laboratory tests increased twice as much as overall hospital costs. Griner also described specific patterns of laboratory overuse, including complete blood counts, serum electrolytes, and blood urea nitrogen (BUN) determinations. X-ray studies of the chest and sputum cultures were ordered as routine daily procedures on all patients in the intensive care unit, and serum glutamic oxaloacetic transaminase (SGOT) was routinely determined on patients with acute myocardial infarction.[3] In another study, expenditures for patients with acute pulmonary edema were compared before and after opening of an intensive care unit (ICU). While mortality rates did not

change, length of hospital stays increased by 2.3 days and expenditures increased by 50 percent. The use of arterial blood gas studies increased sevenfold coincident with the opening of the ICU.[4]

Dixon and Laszlo studied laboratory tests on the medical service of the Durham Veterans Administration Hospital. They judged the usefulness of each test, based on four criteria: Did it generate an order for medication or the need for other care? Were the results considered in planning for subsequent patient care? If findings were abnormal, was the test repeated? If they were normal, was it evident that the test ruled out diagnostic considerations? For a set of randomly selected medical patients, only 5 percent of laboratory tests yielded a positive answer to any of these four criteria. They then arbitrarily limited the house staff to eight laboratory tests per patient per day and found that the percentage of appropriate tests increased to 23 percent.[5]

Schroeder and O'Leary compared the experience of 450 hospital patients of 13 faculty internists who admitted patients jointly at two hospitals, one a major university teaching center, the other a community hospital. After controlling for type and severity of illness, duration of hospital stay was equivalent at the two hospitals. This was somewhat at variance with other published reports and probably reflects the fact that case mix was controlled. The frequency of consultations, laboratory tests and x-ray studies was significantly higher at the university hospital. Of the 54 different types of tests and procedures ordered for these patients, 21 were carried out much more often at one of the two hospitals; 19 of those 21 were done more often at the university hospital, and virtually all of those were blood tests. The increased frequency of laboratory testing at the university hospital accounted for 56 percent of the differences in hospital charges between the university and the community hospitals.[6]

Just as differences in intensity of laboratory use occur among hospitals, differences also exist among physicians. Several years ago, we looked at differences in use of laboratory tests and x-ray studies among similarly trained faculty internists practicing in a university medical clinic. We found huge differences in the costs due to the laboratory tests—as great as 17-fold on one occasion, 20-fold on another, with very large standard deviations.[7,8] We could not attribute these differences to increased severity of cases in the more expensive physicians' practices, nor to characteristics of the patients. Neither could we find any correlation between the increased use of tests and increased quality of care or productivity.[8] In other words, increased cost of practice was not translated into increased quality or efficiency, at least using the measures studied. Similar practice variations have been reported in other settings.[9-11]

In conclusion, five points should be emphasized. First, the increase in medical technology available for patient care and proportion of the population with chronic diseases will almost certainly result in increasing numbers of high cost cases. These cases are likely to account for an increasing proportion of patient care, especially at university teaching hospitals. Second, use of laboratory and x-ray tests is an important component of medical expenditures, and amounts to approximately 25 percent of hospital charges. Third, there is increasing concern that excessive use of laboratory tests occurs in teaching settings. Fourth, great variation exists in the costliness of physicians' medical care, without an obvious translation of these increased costs into improved efficiency of practice. Finally, because of all of these factors, there has been increasing attention to the process of clinical decision making. Articles have recently appeared in major clinical journals that attempt to define in quantitative terms the issues involved in decision making.[12-15] This methodology, sometimes called cost-benefit analysis, means that the financial value of services, care and, ultimately, of patient life is measured in quantitative terms. The problem of how to value a human life is a good point at which to introduce the next case.

Case Presentation

DR. LUBIN:* This is one of several UCSF admissions for a 69-year-old white woman with probable hepatic coma. She has had a history of multiple medical problems: postnecrotic cirrhosis, status postportacaval shunt in 1973, adult onset diabetes mellitus with a neurogenic bladder and multiple urinary tract infections. She had weekly episodes of pre-coma treated at home by her daughter with lactulose, protein restriction, and dioctyl sodium sulfosuccinate (Colace®). Between October 1973 and July 1977, the patient had nine admissions for hepatic encephalopathy. Six days before admission, she became confused and

*Craig Lubin, MD, first-year medical resident.

fell. She became progressively lethargic in spite of home therapy and was brought to the emergency room. The patient was obese, obtunded, moaning and responded only to deep pain. Positive findings included bibasilar rales and a II/VI systolic ejection murmur. The abdomen was obese and nontender, bowel sounds were active and there was no organomegaly. Right gaze preference was noted, her pupils were equal and reactive to light, and she moved all extremities in response to pain. Asterixis was present, deep tendon reflexes were 3+ and symmetrical in the upper extremities, absent in the lower extremities. Pertinent laboratory data included the following: hemoglobin, 12 grams per dl; hematocrit, 35 percent; leukocyte count, 3,400 per cu mm, platelet count, 33,000 per cu mm; prothrombin time, 19.6 seconds; partial thromboplastin time, 41.9 seconds; BUN, 74 mg per dl; creatinine, 2.6 mg per dl; sodium, 138 mEq per liter; potassium, 5.7 mEq per liter; chloride, 104 mEq per liter; bicarbonate, 14 mEq per liter; uric acid, 9.4 mg per dl; normal levels of serum glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase; total protein, 5.7 grams per dl; albumin, 2.3 grams per dl; alkaline phosphate, 131 IU per liter; cholesterol, 107 mg per dl. The urine was positive for bile and negative for glucose, ketones and protein, with 10 to 25 leukocytes and 5 to 10 red blood cells per high power field. On the first hospital day, obtundation persisted in spite of therapy for hepatic encephalopathy. Lumbar puncture showed xanthochromic cerebrospinal fluid (CSF) with 780 red blood cells, 95 leukocytes with 92 percent polymorphonuclear leukocytes per cu mm and a protein value of 133 mg per dl. CSF glucose was 230 mg per dl with a serum glucose value of 470 mg per dl. CT brain-scan was negative for intracranial bleeding. On the second day, blood and urine cultures were positive for Gram-negative rods. The patient was treated with chloramphenicol and gentamicin. Oliguria, sepsis and hypotension developed, and the patient was transferred to the intensive care unit.

On the fifth hospital day, the patient's condition was improving with a rising urinary output and improved mental status, but two days later, liver function tests began to worsen. On the tenth hospital day, urine output began to fall, and findings on liver function tests continued to worsen. On the 12th hospital day, mental status began to deteriorate, and the patient became more icteric. She became increasingly obtunded, with worsening hepatorenal failure, and she died on the 15th hospital day. The hospital bill was $13,836.

Medical Costs—The Ethical Perspective

DR. JONSEN:* The onset of an ethical problem, like the onset of influenza, starts with headaches, pains, and malaise, and sometimes nausea. These problems that we call ethical problems are literally headaches. We find that it hurts to think about them. A medical student said to me the other day, after a class in medical ethics, "These problems make my head hurt." The conclusions we reach after thinking about these so-called ethical problems are sometimes so repugnant to us that they cause a kind of moral nausea. Finally, there is malaise, that vague discomfort and dis-ease, and the inability to mobilize our resources to come to direct grips with the problem. The problems of the high costs of care and of cost containment are already beginning to cause these symptoms. I feel them myself when I participate in discussions of cases in which ethical problems arise.

The first patient discussed today might not require what we are now calling, somewhat pretentiously, an ethical consult, but the second patient might need an ethical consult fairly early. Rather than discuss these particular patients, I will make some general comments.

Examples of the kinds of problems that I am beginning to see are the following: The Medicaid (Medi-Cal) consultant at a major institution starts to challenge and deny charges for certain procedures and days in the intensive care unit because these patients are judged terminal and therefore should not be treated. The criteria for candidacy for renal dialysis are carefully scrutinized by accountants from the Department of Health, Education, and Welfare in terms of quality of life that will result from that procedure. The outcomes of graduates of neonatal intensive care units are carefully analyzed for cost effectiveness. The State Department of Health in California is now asking what is appropriate critical care for the mentally infirm persons confined to institutions. These are ominous points. The most common reaction to these symptoms is beginning to take place, namely

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the formation of committees and the calling of conferences to deal with ethical problems in the allocation of scarce medical resources.

This outbreak of acute ethics, however, should not blind us to the fact that this ethical problem, like a low-grade infection, has been part of medicine since its beginnings. The Hippocratic Oath declares "Into whatever houses I enter, I will come to help the sick." The oath did not oblige the Greek physician to enter every house in which there was sickness. Today we may ask whether some houses cannot be entered because it is not cost effective to do so. Throughout medical history, persons have received care only when they could pay for it, when others (friend, family, the state) would pay, or when a charitable physician would donate care at cost to himself. The finite time of the physician, the limited availability of medicines, and the plethora of sickness and pain all dictated some distribution of medical care in terms of costs. In fact, the scarcity of sanitoria for patients suffering from tuberculosis and other respiratory diseases in the 19th century was a major stimulus toward the establishment of the German health insurance system, the oldest in the world. Some of you remember well the rationing of penicillin in this country, and even more of you recall the rationing of renal dialysis in the mid-1960's. If any event can be credited for the ethics explosion in medicine, it was the effort in the 1960's to give access to hemodialysis on the basis of social and personal qualities. Forgetting that cost has long been the rationing device in medicine, people were outraged by the thought that social status, which of course is often associated with ability to pay, would become the explicit criterion for admission to a lifesaving technology. Yet a committee was established in Seattle to parcel out admission to dialysis on the basis of something more than medical criteria, namely, a set of social worth criteria.

Subsequent debates about federal support of the dialysis program and about national health insurance asserted the right to health care based on need alone. However, it has become patent that need is, on the one hand, a concept of infinite elasticity, and, on the other, a mighty expensive proposition. An ancient ethical question which is part of the debates about the nature of justice is "Should benefits be distributed in terms of merit or need?" We find it repugnant to provide medical care on the basis of merit, as in the Seattle program. Yet we find it impossible to provide it on the basis of need. Impossible because, if we take the need criterion seriously, we find that its costs will withdraw resources from many other necessary and worthwhile endeavors that may have equal claim upon those resources. That is one ethical dilemma about the problem of high costs of medical care. A second centers on the question "Should cost be a consideration at all in clinical decisions?" We say "Life is priceless," that is, you cannot put a price on life. We speak of "cure at all costs"; we speak of the sanctity of life. Of course, we know that these are metaphors, but they are mighty metaphors with a great deal of symbolic power over our motivations, our own self-image, and our cultural mores. How should these metaphors affect decision making? Cost has always been a consideration in clinical decisions. But is this merely a matter of expediency? Is it in fact an appropriate ethical consideration when making a clinical decision to ask "How much will this cost?"

For the sake of an example, I wish to make reference to one tradition, which over many, many years has maintained a strict and demanding position with regard to the sanctity of life and at the same time has a long tradition of considering the problems of medical ethics. I speak of the Roman Catholic tradition, which has always stated that there was a moral obligation to preserve one's health by ordinary means. One of the principal authors in that tradition, Father Gerald Kelly, defines extraordinary means of care in this way:

> Extraordinary means are medicines, treatments, and operations that cannot be obtained or used without excessive expense, inconvenience, or, which if used, provide no reasonable hope of benefit.[16]

That is certainly not the definition of extraordinary means that is common in medicine, which looks at the state-of-the-art rather than at the costs or the inconvenience of the treatment. Yet, in this tradition, which has maintained a conservative view of the sanctity of life, excessive cost is admitted as an ethical consideration relevant to clinical decisions.

This tradition looks principally, however, to the very private kind of relationship among physicians and patients and families. The authors did not explicitly propose how these considerations can be lifted to the level of social concerns. Are cost considerations permissible when clinical decisions are being made in view of social costs

rather than to costs to the individual person? How can we apply these principles to broad social policy?

When some persons who are accustomed to having authority over certain decisions find that authority being taken away or threatened by others, a classical ethical problem emerges. In the 19th century, the two major ethical problems facing Western civilization were problems of that sort. The first was the problem of the relationship between the aristocracy and the people. The revolutions of the 19th century all centered on the problem of authority: Where should it lie? This problem has been solved in fundamental ways by the establishment of modern democracies that provide a very different sharing of authority than existed in the beginning of the 19th century. The second major problem of that century was the problem of the relationship between labor and management. The authority over production and the conditions of work were fought over until finally it was settled that employers have no legitimate authority over the lifestyle of their workers, while they do have legitimate authority over the distribution of dividends. The question of the conditions of labor would have to be negotiated between labor and management. This resolution of the problem essentially redistributed the authority over the conditions of work and the relationship between management and labor. I mention these things in order to suggest that the question of the locus of authority in medicine with regard to clinical decisions is in the same place that the problems of aristocracy and democracy, and labor and management, were in the 19th century.

In medicine, we have not yet begun to parcel out and to discern who ought to have the legitimate authority to do what. It seems to me that the current struggle in which patients' rights are asserted on the one hand, and the involvement of government on the other, with physicians in the uncomfortable middle, is the beginning of a process of parceling out who ought to really make what sorts of decisions. In clinical decisions themselves, which issues should be handled by one with medical knowledge and licensure? One of the major studies of the influences of decisions relative to intensive care, Diana Crane's book *The Sanctity of Social Life,* shows the immense influence of social factors in clinical decisions made to proceed with intensive care.[17] Is this decision appropriately part of a physician's skill and ability?

In conclusion, it seems to me that we need three things in this early stage of considering ethical problems raised by the high costs of care. First, we need an examination of the grounds for the legitimacy of clinical decisions, that is, what appropriately belongs to whom. Secondly, we need clear and general application of appropriate principles for decision making. I frequently have occasion to deal with house staff related to problems of termination of care, and it interests me that even the most rudimentary considerations coming from the tradition of medicine are unknown to many of them. If we are going to teach principles of cost effectiveness to house staffs, as medical school deans suggest, we ought also to teach them ethical traditions and current considerations of the law related to termination of care. Finally, there is need for a set of procedures to say who ought to be making what decision and when. Should the clinical decision be made by a bureaucrat who is not in contact with the patient? Are features of the clinical decision legitimately influenced by bureaucrats who may have a broader view of the issues of cost than clinicians? It seems to me that we have only the most rudimentary beginnings of this kind of distribution of authority at present.

In the last analysis the problem is an ethical problem because it involves a sacrifice by physicians, and when one is asked to sacrifice, ethical problems become extremely acute. The sacrifice is the sacrifice of a great and broad range of authority. The sacrifice is the sacrifice of that great satisfaction that may come with being able to deal with a variety of problems on one's own. And finally, it may be the sacrifice of an image that has always been immensely important to medicine, that is, the image of going all out. There may be times when that is not appropriate.

DR. LEE: *If many of the physicians in the audience think that they are in a bind, our next speaker is in a double-bind.*

Medical Costs—The Hospital Perspective

MR. KERR:* I will assess the implications of federal and state health care cost control efforts for the UCSF hospitals and clinics, particularly from the hospital director's perspective. Most of

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us now clearly recognize that some form of governmental cost control and regulation is inevitable. The exact form this legislation will take is unpredictable at this time, since several bills are pending at the federal level. A California state bill has also been introduced that proposes an inpatient reimbursement limitation quite similar to current Medi-Cal reimbursement limits for outpatient services. In the event that legislation is not enacted at one of these two levels, the issue will possibly be taken to the voters in California as a referendum initiative on next November's ballot.

Previous efforts to control routine hospital costs have been unsatisfactory and somewhat arbitrary. Legislation currently being assessed suffers from some of these same basic weaknesses. The proposed ceiling of 9 percent on total revenues tends to penalize well-run institutions that have historically curbed costs. It fails to give proper consideration to varying lengths of stay throughout the country and, perhaps most important, does not recognize variables related to patient mix and severity of illness. Further, if any cost containment proposal is to reduce hospital costs without reducing essential services, it must recognize a hospital's limited ability to influence some cost increases. General inflation and government mandated programs, for example, are beyond the control of hospitals. Other factors contributing to increases are at least partially controllable, and we must initiate programs to reduce their impact on hospital cost increases.

I am not opposed to reasonable cost or rate regulation. To be successful, however, such a program must have certain essential characteristics. It must set limits on the full cost of hospital care, both routine costs and ancillary services. It must apply to all patients, not simply those whose care is paid for by the federal or state governments. It must be a stable program projected to continue into the foreseeable future. Without such stability, difficult decisions to permanently effect cost savings will not be made. It should be based on a per admission rather than a per diem rate because success in reducing length of stay will naturally result in a higher cost per patient day. There must be provisions for adjustment related to case mix, since the number of costly diagnostic and treatment outputs varies considerably with the nature of the illness. The program must have a reasonable and a timely appeal process to deal with unique situations. Last, it must be simple to administer in a cost-effective and equitable manner. If we are to secure a program with these characteristics, university teaching hospitals have a responsibility to contribute to the legislative and regulatory process. To this end, the directors of the five University of California hospitals are currently engaged in a cooperative effort to review and comment on all proposed cost containment legislation. In addition, we hope to influence the positions taken by national organizations such as the Association of American Medical Colleges and the Council of Teaching Hospitals.

During the past fiscal year our cost per inpatient admission has increased by 11 percent. This represents an improvement over the rate of increase for the previous two years, which averaged 14 percent per annum, and also compares favorably with the increase in per admission cost of approximately 17 percent in the nation as a whole. I can assure you that although we will continue our cost containment efforts from an administrative level, it is highly unlikely that we will be able to operate within a revenue ceiling of approximately 9 percent without modification of clinical activity.

Multiple factors contribute to the cost of patient care in this institution. Some of these factors are essentially beyond our control. Costs that I would include in this category are the following: increases in salaries and fringe benefits for current employees, which are intended to maintain at least modest pace with inflation; sky-rocketing energy costs, and inflationary increases in the costs of supplies, drugs and replacement equipment. Other cost elements can be most appropriately controlled through administrative efforts, but require the continuing involvement of the medical staff. Costs in this category include items such as malpractice insurance, the costs of which have leaped almost 900 percent in the last five years. We will continue our attempts to increase standardization of supply items and to develop joint purchasing agreements with other institutions to mitigate the increase in supply costs. Greater efficiency in some of the support areas, such as housekeeping, laundry, maintenance, billing and registration services, may also be attainable and provide modest cost relief. However, I think that most persons who are active participants in the budget process are familiar with the fact that major efforts already have been made in all of

these areas. In fact, I would suggest that we have been able to remain fiscally viable under current reimbursement limits of Medicare and Medi-Cal primarily through the attainment of greater operational efficiency. Certainly, continuing focus on these administrative elements will be essential. But it appears unrealistic to assume that these efforts, no matter how rigorously pursued, will enable us to live within the revenue limitations likely to be imposed. A major new initiative is required. We must focus on those costs that are most appropriately controlled by the medical staff.

I would like to suggest four areas, each of which represents a substantial component of our expense base, to which we might direct our attention in the future. The first area is diagnostic tests. We are paying more to diagnose illness, because more sophisticated technology is available. In addition, we are ordering more tests. For example, the number of clinical laboratory tests ordered at UCSF is increasing at an annual rate of approximately 10 percent with little change in patient volume. I might add that that 10 percent is a major improvement in contrast with the escalation of laboratory test ordering in the previous two to three years, which was ranging much closer to 15 percent. Many of our diagnostic tools are also quite expensive, both to purchase and to operate. It is often extremely difficult to balance the cost of these services against a significant improvement in patient care quality. In this regard, I am sure that you have found many of the statistics presented by Dr. Schroeder to be not only highly significant, but also alarming.

The second area of interest is nurse staffing. It is being recognized increasingly that levels of required nurse staffing are influenced strongly by ordering habits of medical staff. This factor is borne out in a recent analysis of the relationship between orders and staffing requirements of our intensive care unit. That analysis showed that the work demand on nurses in the intensive care unit has indeed increased, largely due to more sophisticated patient monitoring. But there is no parallel evidence that the patient mix in the intensive care unit has changed substantially, or that our morbidity or mortality outcomes have been affected. Similarly, the increase in laboratory tests referred to earlier has occurred without objective evidence from the medical profession that patient outcomes have been significantly improved. I am not suggesting that this might not indeed have been the case. My only point is that we have been accepting increases in costs of care without requiring objective evidence of increased patient benefits. As difficult as these assessments may be, the public is demanding more than assurance that care has been improved.

A third area in which physician decisions have impact on the cost of patient care are those services provided at the request of physicians by other professional groups, such as physical therapists, respiratory therapists, social workers and so on. With regard to these three areas, I am not suggesting that the ordering of any required services be discontinued, merely that these three categories constitute a major portion of the expense base of this hospital. Each of you must carefully assess the benefits that will accrue to your patients by providing specific services and weigh those potential benefits against the cost of providing the service. You, the medical decision makers, must become increasingly conscious of the cost implications of the decisions you make.

A fourth but somewhat dissimilar area is the manner in which clinical departments schedule patient care and educational activities. It is my strong impression that better coordination of departmental activities with those of the hospital will result in significant improvement in operating efficiency.

No discussion of cost containment in an institution such as UCSF would be complete without mention of the medical education process. Clearly, future research will be required to understand this relationship more fully. The first area that should be addressed in this regard is the hypothesis that the incidence of inappropriate utilization of ancillary services is higher in a teaching setting. To this end, we have held discussions with some members of the faculty concerning the formulation of a study to determine the reasons for which diagnostic procedures are ordered, and the extent to which overutilization occurs. If we determine that overutilization is, in fact, contributing to cost escalation, we would propose developing an educational program to make the staff familiar with our findings. Through such educational efforts and the establishment of a jointly developed monitoring and control program, we could effectively reduce inappropriate demand.

These are some of the specific issues in cost containment. I believe that we all have a common goal in this regard; that is, each of us wants to avoid arbitrary restrictions imposed upon us by

outside forces. There is no question that we will be told that we cannot spend as much to provide our services as we have in the past. The American public seems to be in general agreement with Secretary of Health, Education, and Welfare Califano's contention that hospitals have become obese. It is clear that the health care industry, if not obese, is at least overweight. The question that remains is: Who should prescribe the diet?

Medical Costs—The Policy Perspective

MR. BUTLER:* My function is to summarize what you have heard and then to talk about choices for the future, largely choices for government. You have heard from Dr. Lee that the cost problem has become *the* political health care issue in the United States. You have heard one case history about a set of clinical decisions with a marvelous outcome, but high expense. You have heard from Dr. Schroeder about the difficulty in assessing medical costs around the country; about the influence of the nickels and dimes, the laboratory tests and x-ray studies, and about the enormous differences in practice habits from one clinician to another. You have heard an example of the kind of case that we all know too well—high cost care including intensive care with a final result of death. You have heard Dr. Jonsen talk about how decisions in such cases are and always have been inevitably ethical ones. And finally, William Kerr talked from the standpoint of someone running a hospital and suggested that the end is in sight for him in cutting administrative costs. It is clinical decisions that have to be changed now. My function is to discuss what the government and others are considering doing to change clinical decision making.

Up to present there really has been very little governmental interference with day-to-day clinical decisions. The primary attention of government has been devoted to gross abuse, fraud, excessive facilities, or overlapping or duplicating services in communities. A whole variety of agencies have been spawned to deal with these issues, most notably Professional Standards Review Organizations and Health Systems Agencies. But by and large, their attention has been focused, appropriately at this stage, on major cases of abuse. As you have heard today, the role of these agencies and other governmental agencies has to change. The government stake is too high; the costs are too high. Without trying to be overly dramatic, it is fair to say that the great medical issue of all of our professional lifetimes will be how to deal with the question of clinical decisions, and their impact on costs.

TABLE 4.—*Policy Options for Medical Care Cost Containment*

1. Change consumer behavior
   - Encourage purchase of more cost-effective health insurance
   - Increase cost-sharing through deductibles and copayments
   - Encourage healthier lifestyles
2. Direct governmental regulation of physicians and hospitals
3. Limit supply of physicians and hospital facilities
4. Change method of paying for medical care
5. Change physician attitudes
6. Total government payment for medical care

The six basic alternatives for addressing this question are listed in Table 4. The first is to influence how consumers behave. There are three ways to try to do that. One is to try to change the way consumers buy their health insurance by making them more cost conscious and thereby making them choose the most efficient and least costly kinds of medical care. That is the essence of the recent Enthoven proposal that Dr. Lee mentioned. A quick way to understand the proposal is to look at the rising costs of health insurance for employees of the University of California. The University is paying $66 a month for a family. Comprehensive Blue Cross costs $128. Kaiser Permanente Health Plan costs $82. A small study that we have just begun shows that a number of employees of the University are now electing to move out of the comprehensive Blue Cross coverage to the Kaiser Plan because they would rather pay only $16 a month out of their pockets than $62 for the Blue Cross coverage. Essentially this is the kind of choice that the Enthoven proposal would present to the country as a whole. Another approach is to put more of a financial burden on consumers at the time that they receive care, through deductibles and copayments of one kind or another. This approach is frowned on by many because it affects people at the very time that they are in the worst shape—when they are sick and in the hospital or have lost their jobs. Yet another approach is to try to change personal behavior by encouraging people to take better care of themselves, to engage in more self-care and to follow better health habits. That is a very long process and

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one that we cannot expect to save us a great deal of money in the short run. There are problems with all these approaches. The principal problem with giving people a choice in buying health insurance is that such choices really do not exist in most localities at present. The choices available to employees of the University of California are generally not available nationwide, largely because alternative methods of providing care, such as health maintenance organizations, are fairly limited in their geographical spread. Copayments strike hard at the neediest people. Personal behavior is hard to influence, and efforts to do so run the risk of excessive infringement of personal freedom.

The second alternative to cost control would be direct government regulation of physicians and hospitals. That is what William Kerr talked about, and, clearly, it has been the primary emphasis of the federal government. This approach, which has been taken in most European countries and Canada, includes regulating physician fees and hospital budgets, a very difficult thing to do well. For example, if you regulate the fee for a physician visit, a natural reaction for physicians may be to expand the number of visits. Despite the difficulties, however, this approach is currently the leading contender in government efforts to control costs. A variation of this approach is to regulate the charges of insurance companies, which, in turn, would put the pressure on physicians and hospitals to control costs. This at least has the advantage of insulating physicians from direct action by governmental agencies.

A third alternative, very much related to the second, is to limit the supply of physicians and hospital facilities as well as various kinds of equipment. This is a very possible and very likely alternative now because the government is paying more than 60 percent of the costs of physician training and more than 50 percent of hospital costs and, therefore, has the power to turn on or off the supply faucet. The problems are that limiting capital spending, as it is now proposed, is very hard to do equitably without freezing all the bad aspects of the system, protecting existing hospitals and facilities that may be inefficient, and keeping out more efficient ones. The problem with controlling the supply of physicians is that they tend to work where they want to work in specialties that they choose. Perhaps an even larger problem is the public conception that we have a shortage of physicians in the United States, whereas many who have studied the issue suggest that we have overall a national surplus of physicians.

A fourth option is to change the way that we pay for care. The current system is almost entirely a fee-for-service system. This system might be changed so that physicians are penalized for excessive use of procedures, such as x-rays, laboratory tests and intensive care. This change would be similar to the British system of paying general practitioners through what is called capitation payment. There are problems, of course, in switching to such a system. First, the fee-for-service system is well entrenched in this country, and, if it is changed, a new set of financial incentives would be created, including the incentive to short patients on care. We have had some examples in California, particularly in Los Angeles with prepaid systems for the poor, where that was exactly the result.

A fifth alternative is to try to change the attitudes of physicians and other professionals. Over the long run this may be the most important thing that can be done. But there are also problems here. You are bucking strong professional and economic forces. A physician naturally wants to do as much as possible for the patient. Dr. Jonsen has spoken about that desire, and the cases this morning illustrate it. And there are strong financial rewards for ordering x-ray studies, laboratory tests, surgical operations and other procedures. Schroeder and Showstack have recently constructed a model to illustrate the impact of these economic forces. They indicate that internists in private practice can double or even triple their incomes through increasing their rate of carrying out office laboratory procedures.[18]

Finally, the sixth alternative is government control of most spending. This approach transfers most payment for medical care to governmental budgets, and the government then allocates dollars back to physicians and hospitals and other providers of medical care. Essentially, it is what is done in the British and Swedish systems, and is the approach of the Kennedy-Corman Health Security legislation. It does create the greatest possible pressure for cost control because the costs are coming identifiably out of taxpayers' pockets. The British have been very successful in controlling costs. But the Swedish parliament just keeps voting more money for medical care because of popular pressure by voters for such expenditures. Such an approach has other major

problems. It is hard to allocate the dollars fairly. The rich hospitals tend to stay rich; well-served areas tend to stay well-served; shortage areas tend to stay short. And, of course, there are all of the fundamental problems of any governmental enterprise—bureaucracy, stifling of innovation and lowering of productivity.

In conclusion, some or all of these alternatives are coming in one degree or another. They all have problems and disadvantages. Some will interfere far more than others in the day-to-day lives and clinical decisions of physicians and other professionals. My personal view is that such interference carries such risks to the creativity and vitality of the system that we should concentrate our efforts on options 1, 3, 4 and 5, and try as much as possible to avoid direct government regulation and total governmental payment.

This is going to be a difficult time of transition. Dr. Jonsen has referred to that eloquently. Authority is shifting from the physician to others. Inevitably, with effective cost control, the quality of care as some define it will decline, although I think that this eventuality can be greatly minimized by sensible and flexible approaches. There are, it seems, two great psychological hurdles that all of us have to get over. One requires accepting that we cannot do everything for infants in the neonatal intensive care nursery or for dying patients. Second, and perhaps most important, we must understand that there are no devils to blame, either government or physicians. We have tough choices to make, and we have to get about making them with as much good will as possible.

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Important Advances in Clinical Medicine

Epitomes of Progress — Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in plastic surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Lip Reconstruction After Tumor Resection

EXCISION OF LARGE PORTIONS of lip because of cancer has often resulted in lips devoid of sensation and motion, as well as an incompetent oral sphincter characterized by drooling or abnormal speech. Lip reconstruction traditionally depended upon the use of full thickness flaps from lip or cheek, which were by necessity denervated.

In 1974 Miodrag Karapandzic, a Yugoslavian plastic surgeon, reported a revolutionary technique of lip reconstruction. He separated the orbicularis oris muscle from the surrounding radial facial muscles while keeping the nerve and blood supply intact. The remaining orbicularis oris became a myocutaneous flap suspended by its neurovascular pedicles much like a trampoline. The oral mucosa was left intact. The ends of the muscle were then easily approximated and sutured.

Since the Karapandzic procedure adds no new tissue to the lip, the limiting factor in its application is microstomia. Karapandzic has resected specimens in his series ranging from 3.5 cm to 7.0 cm, and many involved the entire lower lip. Of his 57 patients, secondary procedures for microstomia were required in 13. Jabaley, who popularized the procedure in the United States, has reported excisions with successful reconstructions of 90 percent of the lower lip.

The principle of myocutaneous flaps has been used successfully in other parts of the body. However, this technique is the first to apply this principle to the lip, by showing that the orbicularis muscle and its overlying skin can be freed from its tether of surrounding muscle and used for reconstruction without jeopardizing its nerve sup-

ply. Hence, a functional sensitive oral sphincter may be reconstructed even after resection of a large portion of the lip.

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Jabaley ME, Orcutt TW, Clemet RL: Applications of the Kara principle of lip reconstruction after excision of lip cancer. Am J Surg 132:529-532, Oct 1976

Recent Advances in Maxillofacial Operations

THE MAJOR ADVANCES in maxillofacial surgical procedures for trauma in the past few years have resulted from progress in craniofacial operations. The exposure of the forehead, orbits, zygomatic arches, and upper maxilla and nose made possible via the bitemporal, coronal incision is incredible. Through such an exposure, acute deformities of the upper orbital and forehead area as well as comminuted fractures of the frontal sinus and glabella including "telacanthus" can be reduced and stabilized. The exposure for certain craniofacial separations is excellent. Bone grafting, which in general has been left to secondary procedures in the past, can often be completed so that secondary steps in reconstruction can be obviated. The approach to the upper orbit via the bitemporal incision and via the conjunctival approach to the lower orbit has the additional advantage of less obvious incisions. Similarly, such exposures can be used for late reconstructive procedures.

For congenital problems the most recent improvements in craniofacial surgical procedures have been in reconstruction of certain anterior skull and supraorbital problems in neonates—in general, operation being carried out when the patient is between three and six months of age. At this time there is rapid skull development secondary to growth of the brain. This brain growth can be used to help obtain better skull contour, particularly in cases of plagiocephaly (unilateral cranio-synostosis). Such surgery in Crouzon and Apert syndromes has been less encouraging. New methods for forehead reconstruction have been carried out not only at these early stages but also in the teenage years. A recent advance in forehead osteotomies by Marchac in Paris is very encouraging. He has transposed segments of the anterior skull to create supraorbital rims and better shaped foreheads. Through the use of prefabricated methyl methacrylate implants, we have been able to develop excellent anterior skull contour with protection of the orbits and with minimal morbidity and risk.

There is a great deal of concern by physicians about malpractice from orbital exploration in cases of "blow-out" fracture. In the publications of Putterman, the complications, particularly blindness, reported by him from orbital exploration have caused confusion. This was put into better perspective by the presentation of John Converse at the 1977 annual meeting of the American Society of Plastic and Reconstructive Surgeons in San Francisco. He reported that in his and Byron Smith's series of more than 500 cases of orbital explorations for blow-out fractures there were no cases of blindness. (Other less severe complications could be minimized by careful surgical manipulation and avoidance of excessive retraction.) To generalize and state that in no cases of blow-out fracture should exploration be done is as unacceptable as saying that exploration should be done in all cases. The need for individual treatment of each patient was stressed. Converse pointed out again that, contrary to the opinion of Putterman, the late reconstruction of the enophthalmic orbit is a most difficult and disappointing problem. Close collaboration between plastic surgeons and ophthalmologists is encouraged for the benefit of all, particularly patients.

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Microvascular Reconstruction

WITH INCREASED PROFICIENCY in the techniques of microvascular anastomosis, and success rates greater than 90 percent, the application of this specialized form of surgical operation has extended into the treatment of acute injuries and the reconstruction of posttraumatic and postsurgical deformities.

Patients sustaining traumatic amputation of limbs or digits can be rapidly transferred to centers where microvascular surgical teams are available. The amputated parts are transported in iced saline solutions with the patient. Reimplantation is effected by microdissection of 1.0 mm in diameter donor and recipient vessels using binocular loupes or the operating microscope. Microvascu-

lar repairs are then made using #10-0 or #11-0 nylon sutures under 16 to 25 powers of magnification. Vein grafts are used to bridge vascular defects resulting from crush or avulsion injuries. At the same time, nerve repairs, bone stabilization and tendon repairs are carried out. Postoperative care includes the use of intravenous dextran, occasional heparinization and orally given aspirin. This technique has also been applied to replantation of avulsed scalps, and to transplantation of digits, such as thumb reconstruction by free transfer of a great toe.

Microvascular surgical procedures may benefit those patients with congenital or acquired deformities in whom more classical reconstructive procedures are not applicable or have failed. Full thickness flaps of tissue based on known arterial supply have been successfully transferred by microanastomoses of small arteries and veins. The free groin flap is used commonly in this type of reconstruction and has been employed in the reconstruction of upper and lower extremity soft tissue defects, in repair of facial defects and in breast reconstruction following mastectomy. The groin flap is based upon the superficial circumflex iliac artery. Its course may be preoperatively mapped with a Doppler probe. If suitable recipient vessels can be isolated at the site of proposed reconstruction, the flap can be transferred and anastomoses carried out under magnification.

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Soft Tissue Augmentation With Injectable Collagen

LONG-TERM SOFT TISSUE AUGMENTATION has been achieved by injection of a modified xenogeneic collagen. Studies in rats and rabbits have indicated acceptance of both allogeneic and xenogeneic collagen from human, bovine, rat and rabbit donors. Human clinical trials have been in progress for more than a year.

Dermal collagen is made soluble by controlled digestion with pepsin, a procedure known to reduce antigenicity by removal of nonhelical terminal extensions of the molecule. After purification, an extrudable collagen gel is prepared in physiologic buffer.

After subcutaneous injection the collagen polymerizes as a firm white gel. Within hours there is a pleocytotic reaction. By three days this evolves to fibroblastic colonization and subsequent vascularization of the injected collagen. Over two to twenty weeks, the cellular and vascular distribution approaches the appearance of dense, but clinically soft, connective tissue. Scanning electron micrographs show randomly arrayed, small diameter collagen fibers.

A clinical study of soft tissue augmentation by allogeneic and xenogeneic (bovine) collagen injection has been carried out in 28 patients involving more than 600 individual injections. Contour defects or depressed scars were due to acne, trauma or subcutaneous atrophy; and injections were both intradermal and subdermal. Of 28 patients, there was moderate to pronounced improvement in 24, with follow-up periods exceeding one year. Complications include one allergic reaction and two instances of cellulitis.

Pepsin-modified xenogeneic collagen appears, therefore, to be a promising biomaterial for long-term tissue augmentation.

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Treatment of Basal Cell Carcinoma

BASAL CELL CARCINOMA of the skin is the most common and, at times, one of the most frustrating of skin tumors. It occurs most often in persons over 40 years old and has many causes. It is seen most frequently on the head and neck and other exposed areas of the body. The choice of treatment of basal cell carcinoma depends on the type, size and location of the lesion, as well as the age and health of the patient. Previous treatment must be kept in mind when managing recurrent lesions.

The superficial and early ulcerated lesions respond well to a variety of treatments. Electrodesiccation and currettage, liquid nitrogen, chemotherapy with 5-fluorouracil, radiation and surgical excision have been used. Methods which produce a specimen for pathologic study and determination of tumor-free margins are preferred.

Nodular basal cell carcinoma is less invasive than the ulcerated variety and can be completely excised surgically without difficulty if treated early. The morphea or sclerosing types have very

poorly defined borders and show a higher incidence of recurrence than other varieties. Large and advanced lesions are best treated with wide surgical excisions coupled with reconstruction using local or nearby tissues. Mohs' chemosurgical technique for excision of basal cell carcinoma is receiving renewed interest at present. The complexity and, in some cases, the pain and final scarring limit this approach to the difficult and recurrent tumor.

It is doubtful that a cure can be achieved in patients where deep structures, such as cartilage and bone are involved, but local control usually can be achieved by a combination of surgical excision and radiation. The occasional far-advanced, nonresectable tumor can be palliated with systemic chemotherapy. Results using this technique may last for as long as a year to a year and a half.

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Progress in Synthetic Implants for Postmastectomy Reconstruction

WOMEN WHO HAVE undergone radical, modified radical or simple mastectomy for breast cancer are seeking reconstruction of their deformity in increasing numbers. The results of these reconstructive surgical procedures have improved greatly and the operative steps have decreased with the increased popularity of the modified radical mastectomy and preservation of the pectoral muscle.

Silastic implants are the technique of choice in replacing the missing glandular and adipose tissue, and muscle when necessary. Since their introduction by Cronin and Gerow in 1964, modifications and improvements of synthetic implants have been numerous. Today reconstructive surgeons have a choice of several different types of prosthesis implants, either standard or custom-made for each patient.

The original smooth silastic implant had Dacron® patches for fixation of the implant to the chest wall. These fixation patches have been found to be unnecessary and are seldom used today. Smooth silastic implants come in a variety of shapes and sizes, and are either prefilled with silastic gel or are filled at the time of operation with physiologic saline or dextran. There is also a saline-gel implant which has a central gel-filled compartment and an outer inflatable compartment. Both compartments vary in size. All these implants also can be covered with polyurethane foam, which many surgeons consider desirable because it gives a softer surface for the skin flaps and appears to discourage scar formation.

Today reconstruction of postmastectomy deformities can be done with a high degree of patient satisfaction. This has been made possible by the development of new and improved synthetic implants.

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Myocutaneous Flaps

ONE OF THE most exciting innovations in reconstructive surgical procedures is the development of myocutaneous flaps. These are compound flaps of skin and muscle which can be elevated when the vascular pedicles supplying a muscle also provide perforating vessels from the surface of the muscle to its overlying skin. Such a myocutaneous vascular unit will survive completely even when elevated as an island flap when its blood supply remains intact.

Credit for this advance belongs to McCraw and his associates, who have shown the clinical application of myocutaneous flaps based on the trapezius, latissimus dorsi, biceps femoris, rectus abdominis, sacrospinalis, rectus femoris, gracilis, sartourius and gastroenemius muscles.

Myocutaneous flaps have several advantages over most random skin flaps. First, they may be elevated and transferred without a delay. Second, the muscle provides bulk and padding. Third, the excellent blood supply allows for design of remarkably versatile and safe flaps which are unlikely to undergo necrosis. These features have made these flaps especially valuable for providing coverage for difficult surgical problems such as radiation dermatitis; breast reconstruction following mastectomy; chest and abdominal wall defects; penile and vaginal reconstruction; myelomeningoceles, and open tibial fractures.

It should be recognized that although most skin areas are supplied by perforating vessels from

the underlying muscle, not every area of skin overlying a muscle is suitable for a myocutaneous flap. Design of a myocutaneous flap requires knowledge of the dominant vascular pedicle supplying a muscle and the distribution of the perforating vessels to the overlying skin. It must also be recognized that these flaps require sacrifice of a muscle and its function, that cutaneous sensitivity is variable, and that muscle shrinkage may be considerable in the postoperative period.

Nevertheless, the safety and reliability of these flaps are proven, and their potential is limited only by the imagination and ingenuity of the surgeon.

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Electrical Burns

ELECTRICAL INJURY is the effect of high voltage, current and resistance. At the time of injury, only the voltage is usually known. The greater the voltage the more extensive the injury but currents with potential as low as 110 volts can be a fatal cause of ventricular fibrillation. The injury can affect virtually every system in the body including the central nervous system and the cardiovascular system, and renal function.

Intensity of current is the real danger to life and it is the current flow that produces tissue damage by generation of heat. Alternating current is more dangerous than direct, due to its tetanizing effect on muscle. The longer the duration of contact, the firmer the contact and the greater will be the damage. The smaller the surface area of contact, the greater the intensity of the current and the more severe is the tissue injury.

Electrical injuries are characterized by an entry and exit wound which may be very small and may look misleadingly benign. Delayed necrosis is common. For instance entrance in the hand and exit in the shoulder may proceed to total necrosis of all structures including nerves, muscles and even bones or loss of the extremity.

All electrical contact with voltages greater than 1,000 volts (high tension) require admission to hospital for observation from 12 to 24 hours. Even superficial burns associated with high tension injuries can manifest cardiac arrythmia within this period. In a series of 182 cases reviewed, there was a complication rate of 76 percent. The complications include onset of delayed neurological problems—specifically paresis and sensory changes. Myoglobinuria should be anticipated, and may result in renal shutdown and lethal acidosis. Massive myoglobinuria is treated by debridement of necrotic musculature. Immediate amputation may be necessary to save life. The treatment of acidosis with intravenously given lactate and maintenance of high urine output may prevent renal shutdown. The development of arrythmias should be expected. The most frequent arrythmia seen is sinus tachycardia, which lasts 24 to 48 hours.

Examination of the eyes is imperative to detect early changes from flash burns to the cornea and to document absence of cataracts. Onset of cataracts may be delayed three to six months following injury.

The treatment of the local burn wound frequently requires only small dressings with antibiotic cream or pigskin. However, one should be aware of the frequently associated deep damage to musculature and vasculature. Fasciotomy of an entire limb, opening up all muscle compartments including the volar carpal ligament and extending into the hand, may be lifesaving in severe electrical injuries to the extremities.

In summary, the electrical burn may appear relatively benign but can be a life-threatening event that requires detailed attention to all measures and examination of all vital systems to detect early complications and sequalae.

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Hand Reconstruction in Quadriplegic Patients

SINCE A QUADRIPLEGIC PERSON'S extremities are his most important functional resource, every effort must be made to protect them from insidious events developing in the early injury phase. Proper positioning, elevation, splinting and physical therapy will prevent deformities that may rob a patient of much needed function.

Once muscle recovery is essentially complete, patients should be evaluated by the reconstructive surgeons. From recent studies, three groups of

patients emerge, based not on their skeletal level of injury but on remaining functional resources, both motor and sensory. These groups are the following:

- *Group I patients* (25 percent) have elbow flexion but no or only very weak wrist extension. For an occasional patient, wrist arthrodesis will simplify the type of orthosis from one applied by an aid to one self-applied. Orthosis must remain the basis of treatment.
- *Group II patients* (50 percent) have functional sensibility and strong wrist extension or may attain this through tendon transfers. For this largest group of patients, a strong key pinch between thumb and index can be reconstructed in one surgical procedure for one or both extremities. These patients may benefit from deltoid to triceps transfer to allow precise arm placement. The other digits are left supple for human contact. This is a radical departure from earlier therapy employing multiple joint fusions which frequently resulted in stiff clawed hands.
- *Group III patients* (25 percent) have multiple motor and sensory resources. More refined functions of digital grasp and thumb opposition are possible, though usually requiring multiple procedures. These patients may be functioning at a reasonable level already.

The keys to good therapy include (1) proper timing of surgical operation, generally following stabilization and good psychological adjustment to the injury; (2) individual evaluations to identify motor and sensory resources; (3) carefully done surgical procedures in selected patients, and (4) skilled physical and occupational therapy following operation. Today, 75 percent of quadriplegic patients are candidates for some upper limb surgical reconstruction.

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Subcutaneous Mastectomy

BREAST CANCER will develop in one out of every 13 women, and by the time the diagnosis is made axillary metastasis will already have occurred in 25 percent to 50 percent of these women. These depressing facts have popularized carrying out subcutaneous mastectomy as a possible prophylactic procedure in patients at high risk of developing breast cancer. Since 1974 more than 3,000 subcutaneous mastectomies have been done.

Subcutaneous mastectomy is the removal of all visible glandular breast tissue with preservation of the overlying skin and subcutaneous tissue with or without the nipple and areola. The breast is reconstructed with a silastic prosthesis either immediately or as a delayed procedure.

The major objection to subcutaneous mastectomy is the inability of the surgeon to remove all the breast tissue. With experience however, it is possible to do an extensive procedure taking what appears to be the entire subcutaneous breast, including the axillary tail. Occurrence of carcinoma after subcutaneous mastectomy has been reported and, therefore, the operation must be thorough. It is not a cosmetic operation and must not be compromised to obtain a more esthetic result.

Patients must be carefully selected, well informed and properly motivated for the procedure. The surgeon must be thoroughly familiar with the prophylactic approach to premalignant breast disease so he can inform the patient of the positive and negative aspects of the procedure, the complications and unesthetic results that can occur.

Immediate reconstruction gives the best cosmetic result, but usually should be limited to small and medium size breasts when the amount of subcutaneous fat and the circulation are adequate. Breasts that are ptotic, thin skinned with striae or have multiple biopsy scars are best managed with a delayed implantation weeks to months later. Large pendulous breasts require reduction of the skin flaps and transfer of the nipple either on a pedicle or as a free graft. Placement of the implant under the pectoral muscle is preferred by some surgeons because of the increased vascularity to the skin flaps.

The most frequent complication is skin necrosis necessitating removal of the implant. If this occurs the implant usually can be reinserted at a later time. Capsular contracture around the implant may occur requiring surgical release.

At present subcutaneous mastectomy is done very selectively for indications which include the following:

- Multiple persistent breast nodules in premenopausal or postmenopausal women.
- A biopsy specimen of the breast that shows

intraductal hyperplasia, papillomatosis, lobular hyperplasia or carcinoma *in situ,* noninvasive intraductal or ductal carcinoma.

- A positive family history of breast cancer in a patient who has progressive breast nodularity.
- Increasing anxiety of the patient and her doctor relative to bilateral persistent or increasing breast nodularity.
- Proven malignancy in one breast and nodularity or cystic disease in the opposite breast.
- Suspicious findings on a mammogram in a patient with bilateral nodular breasts.
- Mastodynia, in very carefully selected patients.

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EDITORIALS

The Assault Upon the Professions

JUST A LITTLE MORE than a month ago the President of the United States on a trip to the West saw fit to ally himself overtly and publicly with what is apparently a growing assault upon the professions. Medicine has been an early target, but this time the legal profession was singled out along with medicine. Others may soon be added to the list. That this populist President found it advantageous or even appropriate to place the full weight of his office behind this growing attack suggests that it is not only becoming popular, but may be deeply rooted as well. In any case the assault has had a powerful assist, and may be expected to gather strength and perhaps even some greater element of fury.

If the assault is indeed deeply rooted, it is time to probe what might be the deep roots in order to understand it better. Something clearly has changed. Historically the professions, particularly those persons thought of as making up the learned professions—the clergy, military, scholars, physicians and attorneys—have been somewhat set apart and given both responsibility and authority to do whatever was necessary for the good of society in their fields of supposed competence and expertise. It was as though society recognized that these areas required special knowledge and skills and would be best handled by a segment of society that possessed that knowledge and those skills. This was generally true for the churches, military establishments, universities, and the professions of medicine and law.

But something has changed. Things are not working out as well as they did, or should. For example, in America the churches have been more protected than perhaps in any other nation. They should be thriving but do not seem to be. Our military establishment has certainly been well supported but we seem uncertain about it. We have invested more in our educational system than any other nation but seem to be getting less and less in the way of education for the investment. We have developed and generously supported the most advanced medical science in the world but as a nation we are dissatisfied with the health care our people are receiving and with its cost. And our legal system is clogged, seems unable to cope, and apparently is working more to profit lawyers than to effect a smooth running and efficient system of governance. Clearly, things are not going well in many, if not most, of the areas in which the professions have been assumed to have the knowledge and expertise. No one else knows what to do about the problems either, and it could be that what we are seeing is a national awakening to the fact that the professions have fallen far short of public expectations of their expertise in their fields; a perception by the public that they have failed in their public trust and indeed may have been taking advantage of their privileged positions to feather their own nests. If this analysis is anywhere nearly correct, then the assault on the professions is seen indeed to have very deep roots, is quite understandable and is likely to become more intense before it runs its full course.

But what is it that has changed and where is the true culprit? It is really neither the professions, as the public would like to believe, nor the public, as some professionals would like to believe. It is more likely that modern science and technologic progress, which have brought about unprecedented and as yet poorly understood complexities and interdependencies in every aspect of today's society, are to blame. Neither society nor the professions have given this point its due. It has posed, is posing and will continue to pose problems and challenges with which we are not yet equipped to deal. New attitudes, new approaches, new knowledge and new skills will be necessary.

At the moment there is a growing surge of public frustration and resentment. This is finding expression and outlet in the assault upon the professions, the obvious attempt to restrict or withdraw some of their privileges, while attempting to take over some of the responsibilities previously allocated to the professions which they have

failed to carry out. This will also have to run its course until a new frustration comes about. Paradoxically the same forces—modern science and technologic progress—which created the societal complexity and interdependence with which the professions have so far failed to cope to the public satisfaction, now demand even more specialized professional knowledge and skills to make such a complex and interdependent system work at all, let alone work smoothly. So it is quite predictable that when the present assault has expended itself, society will have to come to some sort of accommodation with a profession such as medicine and the rest of the professionals in health care. This could be sooner or later.

Medicine was the first major profession to undergo systematic public assault. The assault on the legal professions is now official. The educators may well be next, doubtless followed by others. Medicine should now be the first to develop a systematic approach to the very real professional problems that must be solved if the professions are to fulfill the public expectations of them in this new, more complex and increasingly interdependent society. The recent formal recognition by the medical profession of the need for cost containment in health care could be a good beginning.

—MSMW

Lithium Treatment

THE SPECIAL PLACE occupied by lithium among psychotropic drugs has several explanations: the pronounced therapeutic action in mania; the prophylactic action in recurrent affective disorders of the unipolar and the bipolar type—that is, the ability to attenuate or prevent recurrences; the chemical relatedness to sodium, potassium, calcium and magnesium; and the fact that elimination of this drug is determined solely by its renal clearance.

Due to the narrow therapeutic range of lithium, treatment is not particularly simple, and it may involve risk. Lithium administration therefore makes demands on the physician, on his skill and his care. Properly administered lithium treatment may, in return, radically alter the life of patients whose previous existence was dominated by frequent and severe manias or depressions or both. No conscientious psychiatrist can afford to disregard lithium treatment.[1]

In their comprehensive review in this issue Maletzky and Shore emphasize that prophylactic lithium treatment should be given for a long time, perhaps indefinitely. While agreeing with the substance of this statement, I would like to suggest that the prospect is presented to the patients in a different way. "Lifelong treatment" sounds unpleasantly like "lifelong prison," and after all our "sentences" are only statistical. Even if most patients who stop lithium suffer relapse, there are a few who do not, and one cannot predict whether an individual patient might belong to the latter category. I usually say something like the following to my patients: "You have been ill for many years, and presumably you will need treatment for many years. I suggest that you continue the treatment for a period of, for example, four to five years. Then we will take the matter up for discussion again." After such a period some patients have no wish to discontinue lithium therapy; they remember too well the torments before lithium and the bliss during lithium treatment. Other patients feel that their disease might now have come to an end. Discontinuation may therefore be tried under close supervision, in some cases with impunity, in others followed by manic or depressive relapses and resumption of lithium treatment.

Only one alternative to prophylactic lithium treatment seems in existence today: long-term administration of tricyclic antidepressants. The relative efficacies, merits and demerits of the two treatments have not yet been definitively established. At present the evidence indicates that lithium is better than antidepressants in the bipolar cases with both manias and depressions, and that lithium and antidepressants are about equally good in the unipolar cases with recurrent depressions.[2,3] Each of the two treatments has characteristic side effects, and for each there are particular zones of possible risk, the kidneys being in focus with lithium and the heart with antidepressants.

In their discussion of uncommon indications Maletzky and Shore call for controlled lithium trials in premenstrual tension, especially trials comparing lithium with a diuretic. Such trials are in fact on record. Singer and co-workers[4] compared lithium and placebo in 14 women suffering from pronounced premenstrual emotional tension. The trial failed to show any difference between the two drugs. Mattsson and von Schoultz[5] similarly treated women with lithium and placebo but

also gave a diuretic, chlorthalidone. Most of the 18 women showed improvement, but the improvement did not differ among the three drugs. The evidence available today does not support the notion that lithium is of clinical use for premenstrual tension.

Neuromuscular and gastrointestinal side effects seen early in lithium treatment occur during the hours after intake of the drug, at the time when the lithium concentration in serum, and to varying extents in tissues, rises steeply and reaches peak values. It would therefore seem rational to attenuate concentration changes through the use of slow release preparations, and various types of these have been available in European countries for a number of years. A good deal of clinical experience and some systematic studies indicate that this way of administering lithium leads to amelioration of not only the initial side effects but also some of the side effects seen later in the treatment, for example tremor.[6-12] Slow-release lithium preparations do not revolutionize lithium treatment, but they are of distinct benefit to many patients. It is strange and sad that such preparations are not yet available in the United States and Canada.

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The Risks of Climbing

HAZARDOUS SPORT is a way of life of an increasing number of our population. Skiing, hang gliding, scuba diving, surfing, motorcycling, white water boating and mountain climbing are associated with fatalities and, often, distinctive injuries. Wilson and his associates have presented in this issue ("Death on Denali") a careful analysis of the hazards of climbing a big mountain where weather, altitude and hazards of the terrain are important risk factors. Wilson's paper appropriately also evaluates the human factors involved in accidents. This is important since human factors can be modified to greatly reduce death and injuries in mountaineering.

Two general human factors that contribute to most mountaineering accidents are (1) the decision to push on under poor conditions; and (2) lack of proper experience and preparation.

Various circumstances contribute to the "push on despite risk" decision. In many instances it is a compressed time schedule. An expedition must complete the climb before supplies run out or before the monsoon comes (Himalayas). A small party must complete the climb because an airline or work schedule dictates a specific return date. In other instances it is a fierce, competitive attitude that scorns defeat or retreat—a "nothing can turn me back" attitude.

Lack of experience and preparation becomes painfully evident in conditions of bad weather and high altitude. These include inadequate clothing and shelters, lack of knowledge of the effects of rapid exposure to high altitude (pulmonary edema, cerebral edema and mountain sickness), lack of knowledge and experience in proper rope technique and crevasse rescue and lack of experience in decision making on tough climbs in regards to a retreat or a bivouac.

The incidence of mountaineering accidents and fatalities is difficult to determine. On Denali and Mount Foraker the risk of death is about 1.2 percent to 1.7 percent. The incidence of substantial injury or illness in 1976 was 5 percent. In the Himalayas the danger is even greater. During the spring of 1975 every tenth person who took part in a large expedition to Nepal perished.[1] The incidence of altitude illness (pulmonary edema, cerebral edema and severe mountain sickness) on Denali in 1976 was 2 percent with five fatalities. High altitude pulmonary edema occurs in

TABLE 1.—*Major Immediate Causes of Climbing Accidents*

	Percent
Fall or slip on rock	29
Slip on snow or ice	20
Avalanche	11
Pulmonary edema, frostbite, other illness	8
Fall into crevasse	8
Hypothermia	2.5
Contributory causes were:	
Exceeding ability	29
Climbing unroped	22
Inadequate equipment	7
Party separated	3

the lower 48 states as well, particularly in the Rockies.[2] The incidence in persons less than 20 years old is approximately 9 percent but it is lower in adults, being approximately 0.6 percent.[3,4] Deaths due to hypothermia and exposure are occurring more frequently in the western states due to an increasing number of winter climbs and cross-country ski trips.[5,6]

The variety of accidents that can occur in climbing is well documented in Wilson's paper. In 1976 the American Alpine Club received reports of a total of 405 persons involved in 214 accidents in the United States.[7] There were 51 deaths.

The major immediate causes of the accidents are shown in Table 1.

In all, 134 persons (63 percent) were aged 15 to 30 years and 19 percent were between 15 and 20 years old.

This is not a complete survey of all climbing accidents occurring in the United States because only a small proportion of accidents are reported to the American Alpine Club.

Despite these gloomy statistics one can enjoy mountaineering safely and age is not a limiting factor. Ricardo Cassin at 66 years of age was still climbing with big Himalayan expeditions. Richard Hechtel of Redwood City, California, at 64 years of age is still climbing big mountains and in 1975 climbed Illimani in Bolivia (21,201 feet). John Graham of Santa Barbara ascended Mt. Denali (20,320 feet) at the age of 65.

A few general suggestions regarding safety in climbing are appropriate:

- Climb for enjoyment. Do not climb to be a hero.
- Know when to turn back.
- Travel with a guide or an experienced (preferably older) climber. Don't climb alone.
- Climb with good equipment and know how to use it.
- Take a climbing course in theory, methods and practical experience. The Sierra Club, The Seattle Mountaineers and the American Alpine Club hold annual courses on various aspects of mountaineering. Practical climbing courses are offered widely in the western states.

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Modern View of Ataxia

ATAXIA IS A SIGN commonly found as a result of the acute and chronic toxicity of ethanol and of such anticonvulsants as phenytoin (Dilantin®). Even if these cases are not counted, ataxia is a frequent presenting sign of a number of acquired and inherited diseases. Though the inherited diseases as a group occur frequently, many of the individual inherited diseases that give rise to ataxia are rare and are well known only to a few specialists. The first descriptions of the inherited ataxias were recorded more than a century ago and they once helped to make neurology a specialty distinct from internal medicine and from psychiatry. This field, the inherited ataxias and the acquired diseases which mimic them, has only recently matured to an independent status in modern neurology. The underlying disorders have recently been classified, loosely, as defects in oxidative metabolism, in lipid catabolism, in the metabolism of small molecules containing nitro-

gen, and as slow infections from atypical viruses.[1] Few current textbooks discuss the diseases or their biochemical and viral causes clearly and it is difficult to find an adequate list of the acquired diseases that need to be considered in any differential diagnosis.

For these reasons, the major contributions of the Specialty Conference elsewhere in this issue on cerebellar ataxias are a clear, concise synopsis of modern knowledge of the ataxias and a modern differential diagnosis of the acquired and inherited disorders of coordination and balance. While Dr. Dreyfus and his colleagues correctly call their classification arbitrary, any classification today must be arbitrary, given our limited knowledge of the causes and the pathogenetic mechanisms of these diseases. Even with dissension on details, the classification given by the conference is useful in calling attention to the areas of diagnosis and the breadth of underlying problems that must be considered in ataxia patients. In addition, the conference includes brief, but lucid, accounts of the complexities of cerebellar anatomy and physiology, which emphasize the essential points needed to understand the clinical abnormalities.

A few minor points will cause disagreement. The sporadic incidence of late-onset cortical cerebellar degeneration, and of many other "inherited" ataxias, is consistent with incomplete penetrance of a dominant mutation, as suggested in the conference, but it is equally consistent with a recessive mutation or one or more exogenous causes of disease. Most authors[1,2] define Friedreich's ataxia more narrowly than Dr. Vijayan does. Usually the age of onset is limited to a few years before or after puberty. The disease is described as having a recessive or sporadic pattern with ataxia of the legs progressing to the arms, to speech and to the eyes in that order over a decade or more, with impairment of the senses of position and vibration and loss of the deep-tendon reflexes from the time the patient is first examined, with subsequent loss of muscle bulk and strength (in either a distal or a proximal pattern), and with subsequent reduction in the senses of light touch and pin-prick. As mentioned in the Specialty Conference, pes cavus and kyphoscoliosis are almost always found and there is evidence of cardiomyopathy at autopsy, if not before. In fact, the disease is strictly defined pathologically, not clinically.[1,2] The syndrome is associated with dementia even in its early stages.[1-3] Finally, several authors have been more impressed with the signs of mental retardation, dementia or failure of intellectual maturation in ataxia telangiectasia[4,5] than in a-beta-lipoproteinemia,[6] but it is difficult to test mental function adequately in a patient with slow, ataxic movements and speech.

No doubt these differences of opinion will be clarified by further research. Meanwhile, it is important for the patient's sake that physicians recognize the ataxias; know that modern techniques such as radiology, genetic linkage studies and biochemistry can often aid in diagnosis or prognosis; be able to treat according to the precise diagnosis, and be able to refer patients, when appropriate, to centers where clinical research and special forms of treatment may be available.

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CASE REPORTS

Refer to: Wetrich RM, Sidhu DS: Giant sigmoid diverticulum. West J Med 128:539-541, Jun 1979

Giant Sigmoid Diverticulum

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GIANT DIVERTICULA of the colon are relatively rare and, unless the examining physician or the radiologist is familiar with this entity, the preoperative diagnosis may be missed and the surgical therapy ill-timed or misdirected.

Report of a Case

The patient was a 60-year-old man with a five-year history of lower abdominal pain increasing in severity. In the three months before admission he had had three bouts of left lower quadrant pain associated with low-grade fever which was typical of diverticulitis of the sigmoid colon. There was no melena. One week before admission rather severe abdominal pain developed which lasted for about four days before it subsided. A barium enema before admission showed a number of diverticula in the sigmoid colon and an 8 cm round collection of gas associated with the sigmoid colon which did not fill with barium (Figure 1).

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The patient was admitted to hospital. Findings on physical examination were not remarkable except for mild tenderness in the lower abdomen. On rectal examination there was no palpable mass. The hemoglobin value was 14.6 grams per dl and the hematocrit was 46 percent. Analysis of urine showed 10 to 15 leukocytes per high power field. The leukocyte count was 12,500 with 89 segmented cells, 7 lymphocytes and 4 monocytes.

On admission, an x-ray film of the abdomen taken on January 3, 1977, with the patient supine, showed a radiolucent, round, 8-cm structure in the pelvis (Figure 2, *Left*). A film taken with the patient upright showed an air fluid level in this radiolucent mass (Figure 2, *Right*). It was interesting to note that a previous barium enema study done in May 1974 showed only mild diverticulosis of the sigmoid. Because of the history and findings on physical examination and x-ray studies, the diagnosis of giant diverticulum of the sigmoid colon was entertained.

Surgical operation was carried out on December 7, 1976, and a giant diverticulum measuring 8 cm in diameter was identified on the antimesenteric border of the sigmoid colon. This was intimately adherent to a segment of mesentery of the terminal ileum. A sigmoid resection was then done to include the giant diverticulum and an end-to-end anastomosis was done. A segment of terminal ileum was also resected because of compromise of the blood supply secondary to the dissection. Postoperatively the patient did well and was discharged from the hospital on December 16 in good condition.

Discussion

While Hughes and Greene[1] have frequently been credited for first reporting a case of giant sigmoid diverticulum, Harris, Andersen and Wolf[2] in their very comprehensive review point out that Bonvin and Bonte[3] in 1946 described a solitary air cyst attached to the sigmoid colon. Since then, more than 30 cases of so-called giant air cysts or giant diverticula of the colon have appeared in the world literature. These cases are actually

pseudodiverticula of the colon which gradually become dilated by colonic gases trapped within the cyst presumably because of a ball valve mechanism at the neck of the diverticulum. Except for rare occasions,[4-6] these pseudodiverticula are not lined with mucous membrane but, because of the inflammatory reaction, are lined with fibrous tissue and granulation tissue. The giant sigmoid diverticula invariably arise from the antimesenteric border of the colon. Except for one case arising from the transverse colon,[5] all have involved the sigmoid. These pseudodiverticula have varied widely in size, measuring from 6 cm[7] to 27 cm[8] in diameter and except for two cases[9,10] they have all been solitary.

While about 45 percent of these diverticula communicate freely with the colon and fill readily with barium, in others no communication at all is found on pathological examination.[11]

In most of these cases the patients are in the eighth decade of life; six patients have been in their 40's. The sex distribution is about even.

Clinically such patients present with symptoms that are essentially those of sigmoid diverticulitis —that is, intermittent lower abdominal pain, constipation with occasional bouts of diarrhea and fever. Some melena has been reported.[7,12] Nausea and vomiting have been unusual and only one case has been reported with rupture and signs of peritonitis.[13] More than 80 percent of the cases are associated with a palpable mass that is usually movable and may be very tender.

The preoperative diagnosis is not difficult once the supine roentgenogram of the abdomen shows a lower abdominal air-filled lucent structure. Upright or decubitus views of the abdomen will usually show an air fluid level.

These patients have rarely presented as surgical emergencies[12,13] and usually there is ample time preoperatively to prepare the patient adequately.

Figure 1.—Two selected films from the barium enema examination performed before admission show the round collection of gas that is the giant sigmoid diverticulum intimately related to the sigmoid colon. It does not fill with barium. Several usual sigmoid diverticula are also present but these were shown better on other films of the same barium enema examination.

The treatment of the patients in the 35 cases reported in the literature has been quite varied. Two patients apparently were not operated upon.[14,15] In three patients diverticulectomies only were done.[16-18] In one patient diverticulectomy with a transverse colostomy was done.[9] In one patient there was only a transverse colostomy.[13] In two patients resection with colostomies was carried out.[5,14] In 25 cases, sigmoid resection to include the diverticulum was done.

Summary

A 60-year-old man with a five-year history compatible with diverticular disease of the sigmoid colon was found to have a radiolucent mass in the lower abdomen on barium enema. This did not fill with barium. An upright roentgenogram showed an air fluid level in this radiolucent structure. A preoperative diagnosis of giant sigmoid diverticulum was made. A one-stage resection of the diverticulum along with a sigmoid resection was successfully carried out.

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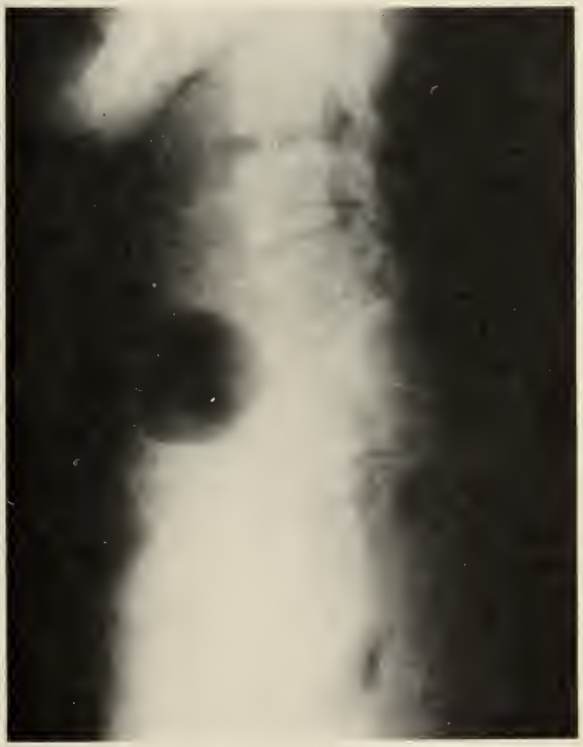

Figure 2.—Left, The supine film from an abdominal series done on admission shows a well defined 8 cm in diameter, round collection of gas in the pelvis. **Right,** The erect film in the lateral projection shows the same air collection with an air fluid level.

Refer to: Riker J, Swanson M, Schweigert B: Esophageal ulceration caused by wax-matrix potassium chloride. West J Med 128:542-543, Jun 1978

Esophageal Ulceration Caused by Wax-Matrix Potassium Chloride

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THE INGESTION of enteric coated potassium chloride tablets to prevent potassium depletion during diuretic therapy has been associated with the occurrence of intestinal ulceration and gastric ulceration.[1-3] There have been recent reports of esophageal ulceration occurring in five patients[4-8] and esophageal stricture occurring in five patients[8-9] following therapy with orally given potassium chloride. In nine of the ten cases, the patients were taking tablets in which the potassium chloride was incorporated into a wax-matrix (Slow-K®),[4-6,8,9] while in the tenth case the patient was taking noncoated potassium chloride tablets.[7] The present case and a review of the other case reports suggest that the mechanism of esophageal ulceration is related to a narrowing of the esophagus usually due to an enlarged heart.

Report of a Case

A 49-year-old white woman with a history of chronic congestive heart failure was admitted to Memorial Hospital, Long Beach, California, on April 29, 1976. She had complaint of cough, shortness of breath, nausea, vomiting, abdominal pain and fever. An electrocardiogram showed left atrial enlargement and an x-ray study of the chest showed a right pleural effusion, and gross cardiomegaly with predominant left ventricular enlargement. A pulmonary angiogram showed a large clot present in a right lower lobe pulmonary artery. Initial anticoagulation was carried out with heparin followed by warfarin sodium (Coumadin®). Other medications included digoxin, furosemide (Lasix®), quinidine gluconate (Quinaglute®), spironolactone (Aldactone®) and potassium chloride liquid. Some heartburn and dysphagia developed on May 22 but improved over the next few days. On May 27 the potassium chloride liquid was discontinued and therapy with Slow-K (two tablets a day) was started. She took two tablets on May 27 but refused to take any more the following two days because of increased difficulty and pain on swallowing. She was discharged on May 29 in a stable but poor condition, being extremely dyspneic with cardiomegaly and chronic congestive heart failure. Her discharge medications included digoxin, quinidine gluconate, warfarin, spironolactone, furosemide and Slow-K (two tablets per day).

She was readmitted to the hospital on June 3, 1976, because of an almost total inability to swallow any food because of pain. Weakness, increasing shortness of breath and confusion were also noted. The admitting diagnosis was cardiomyopathy with congestive heart failure and dysphagia of unknown cause. In spite of increasing pain and difficulty on swallowing, she had continued to take her medications including her Slow-K tablets since her discharge five days previously. The Slow-K was stopped on admission. An electrocardiogram showed a left bundle branch block, inferior lateral fibrosis and left atrial enlargement. An x-ray film of the chest showed congestive heart failure, cardiomegaly and bilateral pleural effusions. An esophagram done on June 4, 1976, showed a polypoid mass measuring approximately 6.5 cm in longitudinal dimension and located at the level of the 6th, 7th and 8th thoracic vertebrae immediately behind the point of maximal compression by the enlarged left ventricle. An upper gastrointestinal study done on April 26, 1976, had shown a normal esophagus with no lesion present. The differential diagnosis of the mass included carcinoma of the esophagus or an ulcerating inflammatory lesion with edematous and inflammatory tissue. Endoscopy was done on June 7 and showed a midesophageal constricting necrotic lesion and esophageal biopsy specimens were obtained. The biopsy findings were reported as benign squamous mucosa and fibrinopurulent exudate consistent with a benign esophageal ulcer. Over the next week and a half the patient noted decreased pain and difficulty in swallowing. A repeat esophagram on June 14 showed an ulcerated mucosa of the esophagus at the level of the 6th, 7th and 8th thoracic vertebrae, the intraluminal component of which had decreased in size since the previous examination. She noted further

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gradual improvement in swallowing and had no further pain when she was discharged on June 20, 1976.

Discussion

Five cases of esophageal ulceration associated with potassium chloride therapy have been reported in the literature. This is the sixth reported case. These six patients and the five additional patients in whom esophageal stricture developed secondary to potassium chloride therapy ranged in age from 33 to 66 years. Nine were women and two were men. Ten of these patients had taken Slow-K. The dosage, when stated, ranged from 1,200 to 3,600 mg per day. The duration of therapy in these patients is not always clearly stated in the case reports but would appear to range from six days (in the present case) to several months of therapy.

A probable predisposing factor in 9 of the 11 cases appeared to be esophageal compression secondary to left atrial enlargement. In four of the patients esophageal ulceration developed[5-8] and in five esophageal stricture developed following cardiac surgical operation.[8,9] In the other two cases of esophageal ulceration, including the present case, cardiac surgical procedures had not been done. The present patient had left ventricular enlargement and cardiomyopathy.

Compression of the esophagus due to cardiac enlargement may result in stasis and dilatation of the esophagus. Clinical and experimental evidence indicates that the local effect of the hypertonic potassium chloride combined with a relative vascular insufficiency is associated with ulceration in the small bowel.[2,10]

Esophageal ulceration secondary to the administration of wax-matrix potassium chloride or noncoated potassium chloride tablets is a potentially serious complication. Death has resulted in three cases. In two patients, cause of death was hemorrhage.[4,8] The other death was attributed to sepsis related to the septic process in and around the esophageal ulcer.[7] Two other patients required feeding via a jejunostomy and later died.[8]

Slow-K induced esophageal ulceration is a potentially serious complication that may develop in patients with esophageal compression. Patients with cardiac enlargement which may result in esophageal compression should not be given potassium chloride tablets. These tablets should also be avoided in patients with esophageal compression due to other causes.

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Refer to: Griswold WR, Mendoza SA, Johnston W, et al: Vasculitis associated with propylthiouracil—Evidence for immune complex pathogenesis and response to therapy. West J Med 128:543-546, Jun 1978

Vasculitis Associated With Propylthiouracil

Evidence for Immune Complex Pathogenesis and Response to Therapy

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PROPYLTHIOURACIL - INDUCED VASCULITIS has been reported previously.[1-6] McCormick[1] established the hypersensitivity nature of the syndrome by showing that the disease recurred when the drug was reintroduced. Inflammatory changes in blood vessels and of skin, liver, central nervous system, pancreas and kidney have been described.

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Submitted, revised, September 9, 1977.

This work was supported by the Bureau of Medicine and Surgery, Clinical Investigative Projects Fund CIP 5-16-445.

The views expressed in this paper are those of the authors and do not necessarily reflect the opinions of the United States Navy.

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Leukopenia,[3] rash, nephritis, arthritis, disseminated intravascular clotting[2] and positive antinuclear antibody[5] have also been observed.

We recently treated a patient with this syndrome, and report the results of immunologic studies and the response to therapy.

Immunofluorescence studies on skin and kidney were carried out using fluorescein conjugated monospecific antisera to IgA, IgM, IgG, C3 and fibrinogen (Meloy Labs). Cryoglobulins were isolated and characterized as previously described.[7]

Report of a Case

A 14-year-old white girl was admitted to Naval Regional Medical Center, San Diego, for evaluation of malaise, fevers and dark-colored urine. She had been well until 18 months before admission when a goiter developed in association with weight loss and lethargy. Laboratory tests showed a thyroxine (T4) value of 14 μg per dl (normal radioimmunoassay, 4.5 to 11.5 μg per dl). She was treated with propylthiouracil, 400 mg per day, and propranolol. Over the next several months the symptoms disappeared and the thyroid gland became smaller. Propranolol was discontinued after two months, but propylthiouracil was continued with no reduction in dosage until admission.

Menarche had occurred at age 12 and menstrual periods had been regular; however, two to three months before admission amenorrhea developed. At about the same time, malaise, low-grade fevers, gingivostomatitis, weakness and weight loss were noted. The urine had been dark red-brown in color for four weeks before admission.

Past medical history was unremarkable. There was no family history of thyroid or collagen vascular disease. On physical examination, body temperature was 39.4°C (103°F); blood pressure, 102/66 mm of mercury; pulse rate, 105 beats per minute; respiratory rate, 21 per minute; height, 66 inches; weight 116 pounds. There was a perforation in the right tympanic membrane. The thyroid gland was diffusely enlarged. Spleen tip was palpable 2 to 3 cm below the left costal margin. The hematocrit reading was 18 percent; hemoglobin, 6.1 grams per dl, and leukocyte count, 1,800 per cu mm, with 12 percent polymorphonuclear cells, 17 percent bands, 64 percent lymphocytes, 5 percent monocytes, 2 percent eosinophils. Platelet count was 200,000 per cu mm, and reticulocyte count was 0.8 percent. Sedimentation rate was 115 mm per hour. Prothrombin time was 13.5 seconds (control 12). Partial thromboplastin time was 32 seconds (control 26 seconds). Total protein was 7.5 grams per dl; creatinine, 1.5 mg per dl; blood urea nitrogen, 21 mg per dl, and serum glutamic pyruvic transaminase, 18. T4 was 6.7 μg per dl (normal 4.5 to 11.5 μg per dl). Analysis of urine showed pH 6.0, protein 4+, glucose negative, hemoglobin moderate. Microscopic analysis showed red blood cells too numerous to count and many red blood cell casts. Urine protein excretion was 1.1 grams per 24 hours. Hepatitis B antigen (by radioimmunoassay), rheumatoid factor, antistreptolysin O, Veneral Disease Research Laboratories and mononucleosis spot

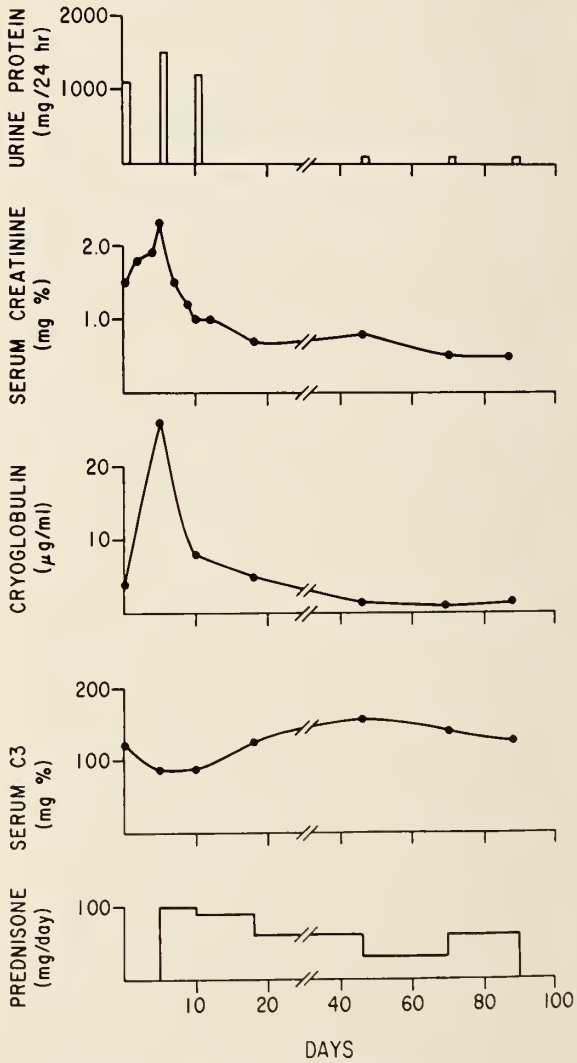

Figure 1.—The response to prednisone therapy. Cryoglobulin is expressed in micrograms of cold insoluble IgG per ml of serum.

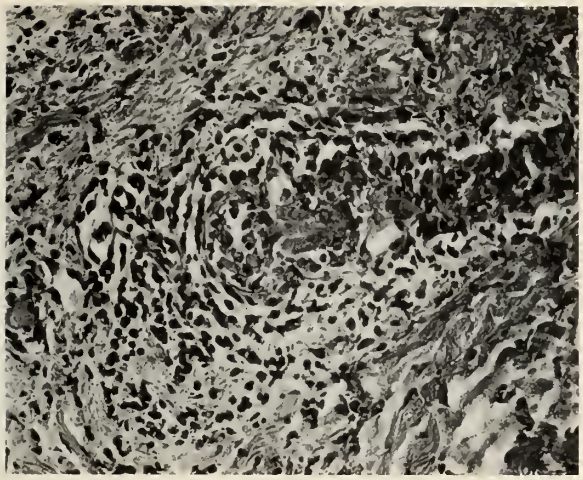

Figure 2.—Representative dermal vessel showing pronounced infiltration with inflammatory cells.

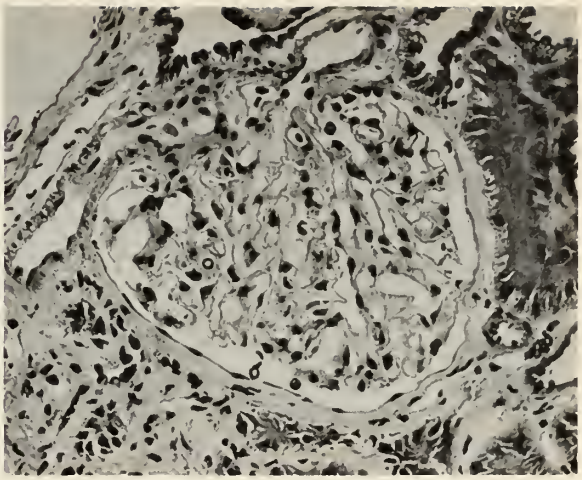

Figure 3.—Representative glomerulus in kidney biopsy specimen taken one week after onset of therapy.

studies were negative. Blood cultures were negative. Throat cultures were negative for β hemolytic streptococci. Antinuclear antibody, LE cell preparation and antithyroglobulin antibody were negative. The following complement studies were done: C3 was 131 mg per dl (normal 90 to 150 mg per dl), C4 was 33 mg per dl (normal 20 to 60 mg per dl), C5 was 11 mg per dl (normal 9 to 13 mg per dl) and total hemolytic complement (CH-50) of 82 units (normal 58 to 103). Quantitative immunoglobulins were as follows: IgG, 2,409 mg per dl (normal 408 to 1,788); IgA, 467 mg per dl (normal 56 to 479), and IgM, 333 mg per dl (normal 50 to 391). A bone marrow biopsy study showed a moderately hypercellular marrow with moderately decreased granulopoiesis and mildly increased erythropoiesis.

Propylthiouracil administration was stopped on admission to the hospital. Over the next five days arthralgias, weakness in the shoulders and trunk, and a maculopapular eruption of purple color covering the legs, forearms, left ear and the dorsum of both feet developed. Reddish-purple raised lesions on the fingers were also noted.

During that time the serum creatinine concentration rose to 2.3 mg per dl, platelet count fell to 56,000 per cu mm, and partial thromboplastin time rose to 45 seconds (control 29 seconds). Fragmented red blood cells were observed in the peripheral blood smear. Serum creatinine phosphokinase rose to 351 and aldolase to 15. A cryoglobulin was isolated from the serum; repeat serum C3 complement was 87 mg per dl (normal 90 to 150). Skin biopsy specimens of lesions on the hand and trunk showed necrotizing vasculitis.

Treatment with prednisone, 100 mg per day, was begun. The patient's condition improved rapidly (Figure 1). Platelet count, partial thromboplastin time and aldolase values became normal in one to two weeks. Hemoglobin became normal in one month. Cryoglobulins disappeared after one month. Administration of steroids was stopped after 90 days of therapy.

The patient has been followed for two years. She is euthyroid, asymptomatic and receiving no medication. Creatinine clearance, 24-hour urine protein, T4 and complete blood count are normal.

Light histology. Skin biopsy specimens taken before steroid therapy showed pronounced perivascular infiltration with lymphocytes, plasma cells and polymorphonuclear leukocytes. Many vessels contained thrombi. Some vessels were frankly necrotic (Figure 2).

A kidney biopsy specimen obtained one week after initiation of steroid therapy contained seven glomeruli. Normal glomeruli (Figure 3), tubules and interstitium were observed. The serum creatinine value at time of biopsy was 1 mg per dl.

Immunofluorescence studies. In skin, deposits of IgG, IgA, IgM and fibrinogen were noted in the walls of the dermal vessels (Figure 4). Albumin control was negative. In the kidney, granular deposits of IgG, IgA, IgM and C3 were observed in the glomeruli (Figure 5). Faint deposits of fibrin were also observed.

Cryoglobulins. A cryoglobulin was isolated from the serum on day 5. It contained IgG, 23.6 μg per ml of serum (normal less than 5 μg per ml); IgM, 31.8 μg per ml of serum (normal less than 10 μg per ml), and IgA, 3.4 μg per ml

Figure 4.—Deposit of IgM in wall of a dermal vessel.

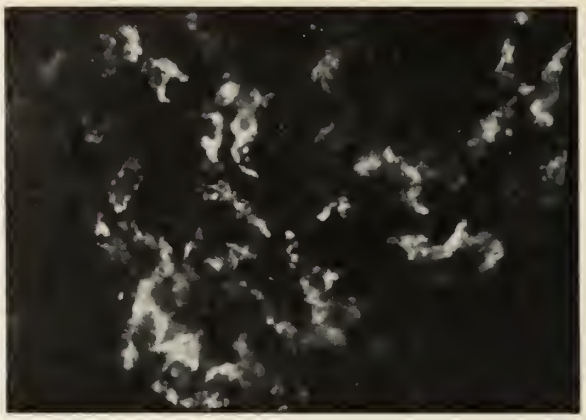

Figure 5.—Deposits of IgA in glomerulus.

of serum (normal, less than 0.5 μg per ml). C3 complement and fibrinogen were not detected in the cryoglobulin.

Discussion

Vasculitis caused by propylthiouracil is a well recognized clinical syndrome. Clinical features include rash, arthritis, leukopenia and anemia.[4] Myositis, observed in this patient, has not been to our knowledge previously reported. Positive antinuclear antibody tests with titers up to 1:160 have been observed in about half of the reported patients. Antileukocyte antibody[6] and disseminated intravascular clotting[2] have been noted. The clinical features of the present case fit the syndrome well and a search for other causes of vasculitis in this patient was unrewarding. Rechallenge with propylthiouracil has produced recurrence of the syndrome and death in other patients and could not be justified in this patient. This patient received a large dose of propylthiouracil for a long period. This may have been an added risk factor for development of the syndrome.

The pathogenesis of vasculitis due to propylthiouracil is not well understood. In the present case the finding of granular deposits of immunoglobulin and complement in the glomerulus and the walls of dermal vessels suggests that the vasculitis is caused by circulating immune complexes. The presence of mixed cryoglobulins, a finding often associated with immune complex disease, adds further support for this hypothesis. These findings have not been previously reported in this syndrome. The nature of the immune complexes is unknown. The drug induces autoimmune phenomena which could result in immune complex formation. Also the drug may act as a hapten, attaching to cell membranes or serum proteins and stimulating antibody production.

The response to steroid therapy in this patient was dramatic. Rash, arthritis, nephritis, thrombocytopenia and cryoglobulinemia, which had worsened before treatment, improved rapidly following initiation of prednisone therapy. Use of steroids may be indicated in other patients with propylthiouracil associated with vasculitis, especially if there is severe involvement of vital organ systems.

Summary

Biopsy specimens from the skin of a patient with vasculitis secondary to propylthiouracil showed necrotizing vasculitis of small blood vessels with intracapillary thrombi on light microscopy and immune deposits in the vessel walls on immunofluorescence. Renal biopsy specimens showed relatively normal glomeruli on light microscopy and granular deposits of immunoglobulin and complement in glomeruli on immunofluorescence. Mixed cryoglobulins were isolated from the serum. The illness responded promptly to treatment with prednisone. These studies support the hypothesis that vasculitis secondary to propylthiouracil is an immune complex disease.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Success Rates in Cardiopulmonary Resuscitation

To the Editor: I have great difficulty writing this letter commenting on the article "Cardiopulmonary Resuscitation in Rural Community Hospitals" by George H. Hess, MD, Carson City, Nevada, in the April issue. It seems almost sacrilegeous to criticize a paper filled with such enthusiasm for cardiac resuscitation and which describes such excellent results. However, I just cannot believe the success rates described by the author. Not only are the claimed success rates as good as those of other institutions, they are better.

There are at least two partly related factors which would influence the denominator in this report. First, in an area as big as the one described, it is highly likely that a significant number of "apparently dead" people will not be transported to a hospital emergency department, but will remain where they are until the coroner or his representative comes to the scene and pronounces them dead. Second, it is unclear what proportion of all people who die in the hospital have resuscitation attempted. It is possible that an aggressive, "no code" policy or similar policy to easily identify those who should not be resuscitated would result in a significant reduction in the denominator of the success equation. Adding in the eight persons who were excluded because the likelihood of their recovery seemed extremely low, the survival rates decreased by 5 percent.

Unfortunately, the author has used a relatively vague end point for his review; namely, he regards a successful resuscitation as one that results in the discharge of the patient from the hospital. It is important to document the mental and physical abilities or disabilities of survivors of cardiac arrest when measuring success rates. However, I will venture a guess that the disability level of the author's survivors is quite close to their precardiac arrest level, since recent data appear to indicate that the number of brain damaged survivors is relatively small. My hunch is that the unusual and hard to believe success rates of this report are related more to the size of the denominator than to anything else.

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* * *

Dr. Hess Replies

To the Editor: In response to Dr. Eliastam's comments, I would like to present some additional data to allow the reader to judge the article better. However, I must agree with Dr. Eliastam's two basic criticisms, which would be true of any study similar to the Carson City study. In addition, I would like to point out that the first criticism was acknowledged in the conclusion of the paper and that such data would be impossible to retrieve retrospectively.

With respect to the second criticism, requesting information on the total number of deaths in the hospital, I would like to supply the following information. During the 22 months covered by the study, there were 8,671 admissions to the Carson-Tahoe Hospital. During this same time, there was a total of 131 deaths in the Emergency Room and In Patient Services. Of these 131 persons, 52 (40 percent) underwent cardiopulmonary resuscitation (CPR). While 79 persons died without CPR, I can state categorically that the hospital does not pursue an "aggressive, 'no code' policy" because such decisions are made solely by the patient's personal physician. I have reviewed 22 consecutive charts of patients who died without cardiopulmonary resuscitation during the study, and most died of terminal metastatic carcinoma or other irreversible medical conditions.

I will leave it to the reader's discretion as to whether or not to include all or part of the additional 79 deaths in the "denominator."

I also would like to point out that the total number of patients involved in the study is a relatively small group as compared with other studies, and I am not sure that the differences are statistically significant. However, I would like to point out that the Seattle experience has suggested that when CPR is initiated by a trained bystander, nearly 40 percent of the patients will survive to leave the hospital alive.

In any event, it is still my contention that these criticisms do not alter the conclusions of the paper. In addition, I still feel that the paper shows that aggressive cardiopulmonary resuscitation will result in a significant number of survivors and that programs to implement effective CPR in rural areas and smaller hospitals are beneficial.

GEORGE H. HESS, MD
Carson City, Nevada

Local Physicians, PSRO's and HSA's

To the Editor: The editorial in the April issue on Health Systems Agencies (HSA's) and local physicians was pertinent, but I don't think that it fully explained physician input in the planning process.

The editorial stated that "The omission, almost to the point of exclusion, of a significant presence of practicing physicians at each level of planning and decision making under this law seems to be a flaw which may prove serious and could even be fatal." And further, it said "Physicians have been assigned a peripheral rather than a central role."

What the editorial failed to mention was that physicians are involved all the way on Professional Standards Review Organization boards. Furthermore, by federal request we do have a memorandum of understanding with the HSA's. What does this mean?

It means that we can and will divulge nonconfidential data to HSA's to help them in their planning process. For example, data can be collected on computerized axial tomography (CAT) scanners as to their overutilization or underutilization. In addition, data can be collected as to whether our physicians thought the tests were better on the CAT scan or with use of ultrasound. Similarly, data could be developed regarding intensive care units, coronary care units, neonatal care and emergency rooms.

The skilled nursing facility has become a problem because of the paucity of beds—primarily because of the low Medi-Cal payments. Data could be accumulated to show whether this, in turn, causes more money to be wasted on acute hospital beds.

Of interest is the fact that in our HSA-PSRO community, there is a PSRO slot on the HSA board.

For the above reasons, I think that full participation by physicians in their PSRO is the only way to balance the consumer-dominated HSA.

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A New Dimension to Medicine

To the Editor: I was pleased to read the editorial in the April issue ("Health Systems Agencies and Local Physicians") urging increased physician involvement with health systems agencies (HSA's). I have been intimately involved with the local agency in my area but have found it distressingly frustrating when it comes to alerting local physicians that it is to their advantage to be involved from the initial stages with any such project. When physician involvement is present it is usually in reaction to a proposed plan of action—a tactic that, more often than not, is late and often has little success in amending the proposal. It is like the proverbial closing of the barn door after the horse has bolted.

Lest the editorial provoke an outburst of enthusiasm, let me inject a note of caution. The work can be pure drudgery most times; there is nothing glamorous about it. As the editorial noted it can often be wearing, time consuming and frustrating. Intelligent, diligent, nonself-serving input from physicians, however, can be significant and will often be welcomed.

There is a new dimension to medicine and this involves becoming more active and acquainted with legislation affecting the future of medicine. This means a definite commitment in time and effort. This could be done individually or in conjunction with the efforts of the local county medical society.

An aggressive leadership role has to be assumed by physicians. Participation in HSA activities need

not be limited to the governing body. There are multiple avenues for participation: serving on sub-area advisory councils, task forces and committees, or attending meetings as observers. This allows physicians to become part of the decision-making process that could finally achieve a mutually agreeable solution.

The recommendations of health planning agencies can have a significant impact on health care services in many communities. At present the HSA's monitor and regulate all major expansion programs within the health care system so that costly duplication of services can be avoided while necessary services are maintained. Eventually they will assume responsibility for reviewing the appropriateness of existing health care services for their respective areas.

Local HSA's respond to local conditions and at present are controlled by the local community. Physicians have an enormous stake in seeing that they succeed because, as Dr. John Freymann—the President of the National Fund for Medical Education and himself a physician—has noted, providers have the most to lose if these local agencies fail.[1] The alternative to provider inertia and local agency failure would be monolithic control of the entire health care system from Washington.

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Psychogenic Rheumatism

To the editor: Dr. Michael Reynolds' excellent article on psychogenic rheumatism in the April issue again reminds us that musculoskeletal symptoms can be a somatic expression of emotional problems.

However, I would disagree with his statement that the distinction of psychogenic from organic disease "should not be difficult." The concept that many of these symptoms "fail to correspond to patterns of organic disorders" implies that the patterns of organic disorder are all clearly and completely understood at this time. I do not feel that this is an accurate conclusion. I agree with Dr. Reynolds that the diagnosis of rheumatoid arthritis and its variants is often used indiscriminantly, yet am concerned that the concept of psychogenic rheumatism may not also become overused and abused. It is soothing, unfortunately, to physicians to label illnesses as idiopathic or functional rather than to admit the limitation of current diagnostic methods. This is dangerous, not only because of the social implications for the patient, but also because it tends to decrease a doctor's diagnostic alertness to newer patterns of organic disorder and to those that await discovery. This was well expressed by Jean Marie Charcot (1825-1893) who said "In the last analysis, we see only what we have been taught to see. We eliminate and ignore everything that is not part of our prejudice."

MICHAEL DAVID ROBACK, MD
Los Angeles

Of Pediatrics and Geriatrics

To the Editor: Dr. Alex Comfort's commentary "Geriatrics—The Missing Discipline?" (West J Med 128:257-259, Mar 1978) and his numerous contributions in similar vein, prompt me to put on paper thoughts I have had for some time now.

I agree that medicine (and surgery) of the aged is different than for adults, just as pediatrics is different. Indeed pediatrics is more related to geriatrics (and vice versa) than either is to adult medicine. As far as these two specialties go, it is true that certain diseases are more or less confined to one or other extreme of life. But there are many that afflict both age groups in similar manner. Examples are pneumonia, electrolyte disturbances, metabolic diseases and acute conditions of the abdomen, to name a few. Furthermore, there is no reason why one medical specialist could not become expert at those conditions which are common to both groups, as well as congenital and degenerative diseases which afflict pediatric and geriatric patients respectively.

The presentation of major disorders becomes increasingly nonspecific at both extremes of age. Furthermore, in childhood as well as in old age, most people are "well" despite minor continuing conditions; as Hodkinson, quoted by Comfort, says, a common syndrome in the elderly, is the equivalent of "failure to thrive" in pediatrics.

Another great similarity between the two disciplines is the dose range of, and the response to, commonly used medications as well as the complications of these medications.

With the dwindling of the pediatric population and the parri pasu increment in the ranks of the elderly, a marriage between the two disciplines

would also have logistic merit. A number of pediatricians have deserted the ranks to become family physicians; an organized flow into the combined specialty of pediatrics and geriatrics would appear to be a natural solution to this problem in the short run. In the longer view, a combined pediatric-geriatric residency could produce physicians well-rounded in both these fields.

There could be some objection raised to housing the patients in the two extremes in the same unit within a hospital, but this need not apply. Similarly there may be objection to having these patients in the same waiting room in the doctor's office, but this too could be avoided or lessened by having separate waiting areas.

I offer this suggestion to the pediatricians of this country not at all in jest; they have a golden opportunity to salvage their profession and indeed to enhance it by taking on the challenge of the medical care of the elderly who now, as Dr. Comfort points out, are the pariahs of medicine and of society in general.

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Lincoln's Health—Dr. Schwartz Responds

To the Editor: My recent article, Abraham Lincoln and Cardiac Decompensation (West J Med 128:174-177, Feb 1978) concerned itself only with heart failure, the evidence for the related diagnoses of the Marfan syndrome and aortic insufficiency having been reported years ago.[1,2] In spite of this, Dr. Walter T. Flaherty of Tustin, California cites the latest report in rejecting the diagnosis of the Marfan syndrome while strangely accepting the diagnosis of aortic insufficiency (Correspondence, West J Med 128:352-353, Apr 1978). Actually, the diagnosis of a valvular lesion is untenable in Mr. Lincoln unless he did indeed have the Marfan syndrome—his "Wasserman" was negative.[3]

Regardless, Flaherty's refutation of the Marfan diagnosis is based extensively on the statuary of Lincoln—these disclosing, he states, no eye or skeletal deformities. I offer in this regard a quote from a classic study: "There are sculptors of the very highest rank who have declared . . . that . . . Lincoln is not a proper theme for sculptoral treatment . . . the unique problem . . . [is] . . . representing Lincoln's lank awkward figure . . . in a . . . work of art."[4] Despite this, many sculptors have made the attempt, some even portraying him as an Adonis, while Vinnie Ream—the sculptor Flaherty extols—depicted the President in a Roman toga. Other scuptors met the problem; Barnard's statue intended for London caused an international furor with its realism—the large hands, the big feet, the awkward pose—which found warm acceptance by an English consultant, George Bernard Shaw.

As to the casts of Lincoln's hands negating the diagnosis, a careful review of the original genetic-morphologic report[1] will show that the casts were specifically and most objectively considered by referring to an earlier, independent, anthropometric analysis of the hands by their custodian at the Smithsonian Institute. The data were found analogous to and consistent with an abnormal metacarpal index as calculated in the Marfan syndrome from an x-ray study of the hand, this retrospective "reconstructed x-ray" for Mr. Lincoln, as well as the Marfan diagnosis, being accepted editorially in 1964 by the *British Medical Journal*.[5] Contrary to Flaherty's opinion, one can readily find reference to bony deformities of Lincoln's chest—his law partner clearly described it as a "sunken breast,"[1] that is, a pectus excavatum. Also, Lincoln did discuss his eye problems, both with his secretary John Hay and with a reporter, Noah Brooks, and revealed to them his two curious episodes of diplopia. Finally, hypertropia of the left eye was described by the President's contemporaries and is apparent in his photographs, if not in the more flattering statuary.

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Refer to: Tsuei JJ: Eastern and Western approaches to medicine.
West J Med 128:551-557, Jun 1978

Special Article

Eastern and Western Approaches to Medicine

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An objective comparison of Eastern and Western approaches to medicine is necessary to further evaluate the validity of Oriental medical techniques such as acupuncture. The development of medicine in Western nations follows the way of hypothetical deduction and the Eastern approach uses the inductive method. The Western approach clearly divides the health from the disease, yet the Eastern approach considers health as a balanced state versus disease as an unbalanced state. The Western approach tends to change the environment and the Eastern way is to prefer to adapt to the environment. There are numerous difficulties in comparing these two approaches. The same terminology may apply to entirely different facts, the teaching and learning methods are quite different, and the evaluation of the treatment is almost not comparable.

In order to help understand the Eastern approach better, an understanding is needed of the basic Chinese concepts: the concept of a small universe living in a large universe; the duality concept of yin and yang; the concept of anatomy; the concept of physiology in Chinese medicine—the state of equilibrium expressed by the five elements; the concept of pathophysiology expressed by the external and internal insults; the concept of maintaining and promoting health expressed by the circulation of chi *and* hsieh; *the therapeutic concept in Chinese medicine—the normalization or reestablishment of balance of the body function; the concept of preventive medicine.*

Two western states in the United States, Nevada and Hawaii, have regulated acupuncture as an independent practice not requiring medical referral or supervision.[1] Two other states have ruled that acupuncture can be practiced under the supervision of a licensed physician as in Oregon[1] or by physician's referral as in California.[2] This seems to indicate that the possibility of acceptance of the practice of Oriental medical techniques by the profession and the general public in this region is promising. There is, however, a great variety of contrary opinions about acupuncture within the medical profession which is reflected by the diverse legislations in many states. An objective comparison of Eastern and Western approaches to medicine may well shed some light on the true value of Oriental medicine and help to integrate this approach into our modern medical practice.

Western medicine has developed through hypothetical deduction. Every statement in Western medicine is a result of a series of fact probings.

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The hypothesis is usually derived from general observations of a phenomenon and a research plan is carefully designed. When enough data are collected, conclusions are drawn as a result of critical statistical evaluations. In contrast, Eastern medicine uses the inductive method. Oriental medical literature in general is a record of practical experience accumulated from millions of practitioners throughout thousands of years. The format of recording is a result of direct observation. This makes it difficult to compare the results of the two different approaches to medicine.

The Western approach to medicine clearly divides health from disease, and the main emphasis is on the individual body. The environment is considered as only one factor that affects the body. Responsibility for various phases of health and disease care is shared by professionals in several disciplines. Physicians are trained mainly for the care of acute phases of disease, that is, disease detection and therapy. The areas of health promotion, disease prevention and rehabilitation are taken care of largely by other trained professions.[3] This team approach gives the impression of being more community-minded than individual-based, yet the objective is still individual well-being. The Eastern idea of health and disease is looked upon as the two sides of a coin. In other words, every individual person is in a state of balance between external insults and internal defensive mechanisms. If the insults are greater than one's defenses, one is ill; if not, one maintains good health. Since the individual person is considered merely a microcosm existing in a macrocosm, there are changes every minute, with constant readjustments. The duty of a physician is to strengthen the internal defensive power and power of adaptation of each individual person and enable him to fight the environmental insults, or to adapt to external changes so that he can live in peaceful balance within himself and with his environment, thereby maintaining good health. The responsibility of a physician is, in fact, to promote health and treat diseases when they occur.[4]

The Western approach to health care involves, among other things, changing the environment in which we live. For example, if the weather is not ideal for the body, a shelter is built with temperature control; if the atmosphere and humidity are not comfortable, other controls are added. Antibiotics are developed to counteract bacteria harmful to the body. Sterilization techniques are practiced to shelter from the bacterias. In therapy, the same principles apply. Artificial limbs and organs are used to replace diseased or injured body parts. Synthetic hormones and vitamins are used for impaired bodily functions. These achievements mark the victory of science and wisdom of mankind. However, in spite of the fact that human life is being prolonged, and the handicapped and retarded are functioning, the majority of people may be free from serious disease but not from discomfort or pain, either physical or mental. In other words, people are still suffering and unhappy. The Eastern approach may be passive toward, or may simply ignore, the idea of converting the environment. Its emphasis is from the "within" to strengthen the enormous defensive and adaptive powers of one's body so that the latter may accommodate physical or mental stress. It may work slowly and appear to be less effective; but, if successful, the result usually is a balanced, comfortable body and a happy person.

With all the dichotomies mentioned above, it follows naturally that the learning systems and the terminologies used must be different. Even if the same terms are used, they may, perhaps, have quite different meanings.

The Western approach looks into every aspect of a person with great detail, from a microscopic to a macroscopic view of biology, embryology, histology and microbiology, studies the cellular level of chemistry and physics, then looks to the basic anatomy and physiology, and finally moves to the clinical practical aspects of internal medicine, surgery, pediatrics, obstetrics and gynecology, psychiatry and public health. With this large field in such minute detail, no one can master everything; therefore, training and practice tend to be segmented.

In the Eastern approach, the learning process begins with the universe. The laws of nature find a parallel in bodily phenomena; the Eastern medical student must, therefore, learn astronomy and geography: "If in curing the sick you do not observe the records of heaven nor use the principle of earth, the result will be calamity."[5] "If you understand the period above; the writing of heaven (astronomy) below; the principles of earth (geography) and in between earth and heaven; the affair of man, then may you live a long life."[6] The system of the body is classified in a way quite different from that of Western medicine. So too, are the other aspects of medicine. For

instance, the body is divided into 12 anatomical, physiological and psychological units. The causes of disease are divided into six environmental insults and seven internal insults. All the diseases are represented by symptom groups or syndromes. This approach may appear oversimplified in matter. In addition, the much smaller volume of written statements and literature, the writing mostly in the form of inductive recording, may appear easier to learn and largely philosophical in approach. However, this leads to the necessity for more clinical observations and practice and longer periods of individual teaching on a one-to-one basis. Even with all the differences, Western-trained physicians can clearly see that the Eastern approach emphasizes knowledge in terms of environmental health, surface anatomy, functional physiology, neurophysiology and the psychosomatic aspects of medicine, although different terms are being used. After learning the differences, students may be able to make a fair judgment of the validity of either the Eastern or Western approach to medicine and take advantage of knowing both.

The Chinese Concept

Since the readers are largely Western-trained professionals who are familiar with the Western approach in medicine, this section will only categorize the Eastern concepts.

The Microcosm Living Within the Macrocosm

In Chinese medicine a human being is looked upon as a small universe. The anatomical structures and the physiological functions of the body are correlated with one another. They also correspond and react to the outside environment—the large universe. When everything coexists in perfect harmony, a person is in excellent health. Since the physiological process is in continual change and balance, as are the environmental conditions, this delicate change and balance between the small and the large universe are constantly being readjusted in every respect. Once the balance is disturbed, illness sets in.

In one chapter of Ling-Shu in the ancient *Nei Ching* (or Canon of Medicine),* it says:[7]

"Man is nothing but a creature living between the heaven and the earth."

"Atmosphere is what Heaven bestows on us; Produce is what Earth bestows on us. Life is a product of the interaction between the atmosphere of Heaven and the produce of Earth; and reproductive energy is the source of life. The spirit comes about as a result of a struggle between the two reproductive energies (the beginning of life); the physical strength (the body) is the element that is responsible for the performance of activities. Sentiment (the soul) is the element that directs the mind to perform activities.

"Therefore, a man of wisdom will live his life in accord with the four seasons and in line with cold and hot climates keeping peace with the environment; he will live a harmonious life of joy and anger in a peaceful manner keeping peace within oneself; he will maintain a balance between yin and yang, between robustness and tenderness. Consequently, a man of wisdom will not be susceptible to attack from vicious energies and he will live a long life."[8]

The Duality Concept in Chinese Medicine—Yin and Yang

Yin and yang are two basic fundamentals of ancient Chinese philosophy. First described in the *I Ching, Book of Changes,* they are opposite terms representing the duality of positive and negative power. Normally they are equal in value, in balance with each other, and cannot exist one without the other.

In the classical Chinese medical literature, yin and yang are used to describe the state of equilibrium within and around the body, its organs and functions, and the relationship to the environment. The following illustrates this application:

- *The Beginning of Life*

  "The origin of life started with yin (female) and yang (male)."[9]
- *Structure of the Body*

  "When speaking of yin and yang, the exterior is yang, the interior is yin; when speaking of yin and yang in the human body, the back is yang, the front is yin; when speaking of yin and yang of the organs in the body, the solid organs are yin, the hollow organs are yang."[10]

"Therefore, the heaven is yang and the earth is yin; the part of the body above the waist is comparable to the heaven while the region of the body below the waist is comparable to the earth."[7]

**Huang-Ti Nei Ching (The Yellow Emperor's Canon of Medicine)* was originally published in two volumes, in which the Ling-Shu describes the theory and the Su-Wen discusses the practical aspects of acupuncture and moxibustion. Chi-Bai is thought to be Huang-Ti's medical officer. From the geographical names, literary construction and historical allusions, it may be assumed that the *Nei Ching* was published about the end of the Chou dynasty (1121-249 BC) or the beginning of the Chin dynasty (221-207 BC). The contents are naturally much older. Evidently it is not the work of a single person but a compilation of various writers.

Since the meridians, functional tracts of the body, running on the outer surface of the extremities are called yang meridians and the inner surface are called yin meridians, the outer surface is yang and the inner surface is yin.

- *Activities of the Body*

  Yang represents the active, strong, fast and positive aspects of the body. Yin, on the other hand, describes the passive, weak, slow and negative nature of the being. As a matter of fact, all of the visible organs and structures of the body are described as yin because of their passive nature when they are not functioning. The organs classified as yang are so named because they exist only by activity.

  "Yang results in spirit, yin gives the shape."

  "Yin in the interior is the guardian of yang; yang in the exterior is the activator of yin."[5]

- *Diagnoses of Diseases*

  "So to explain the yin and yang, hypofunction is a yin disease, hyperfunction is a yang disease. Chronically inactive is yin, acutely active is yang. Limpering, weakening or decaying is yin; hasty flourishing is yang."[11]

- *For Treatment*

  "In yang diseases, treat the yin; in yin diseases, treat the yang."[5]

- *In General*

  It seems that everything in life can be classified according to its yin and yang components.

"The relation of yin and yang is the means whereby the myriad of things are able to come to birth; yin and yang react upon each other, producing change."[5]

To further prove that the words yin and yang are used merely as symbols, it is said "now the yin/yang have a name but no form. Thus it can be extended from 1 to 10, from 10 to 100, from 100 to 1,000, from 1,000 to 10,000, etc. It can embrace all things."[12]

In order to be able to express all the phenomena, the yin and yang components not only oppose but also contain its opposite. "There is yin within yang and yang within yin. From dusk until midnight, the yin of heaven is the yin within the yin. From midnight until dawn, the yin of heaven is the yang within the yin."[10]

This idea is best illustrated by the symbol (Figure 1) where there is a small black dot in the white half and a white dot in the black half.

By now, readers may realize the similarity of the expressions of many phenomena in Western science. The most obvious ones are the positive and negative electrical charges, the levorotatory and dextrorotatory chemical compounds, the acid base balance and the reciprocal phenomenon of the hypothalamic-pituitary-gonadal axis.

Figure 1.—Yin (left) and Yang.

An interesting illustration of yang within the yin and the yin within the yang might be the fact that there are androgens (male hormones) existing in women and estrogens (female hormones) existing in men.

The Concept of Anatomy in Chinese Medicine

Since the Chinese divide the body into parts by their functions rather than by their structure, the three components of the body—the anatomical, physiological and the psychological—are linked by an abstract term, meridian. Many Westerners thought the Chinese did not know true anatomy. The fact is that even in the Yellow Emperor's (Huang-Ti) first book it was stated: "at first, the embryo is brought into being by a combination of two reproductive energies, yin and yang; and then the marrow in the brain is formed and the bones are formed in order to support the body; and then the meridians are developed in order to transmit energy and blood; and then the tendons are formed in order to sustain the bones; and then the muscles are built in order to serve as the walls of the body; and then the skin becomes solid and the hair grown. After the baby is born, the stomach begins to take in food, the meridians begin to function, and the blood and energy begin to circulate in the body."[13]

"As to the man himself who is only eight feet tall on the average [Chinese feet], the external size of his body is measurable because its skin and flesh are nearby, and also his pulse may be taken in different regions. In addition, when a man dies, his body may be dissected for observation. For this reason there are established standards by which we determine the hardness and crispness of the viscera, the size of the bowels,

the quantity of food consumed, the length of meridians . . . All these aspects of the human body as outlined above are governed by a set of established standards. Therefore, these standards also govern the techniques of acupuncture therapy and moxibustion therapy."[7]

Since we know that the Chinese did understand anatomy, this way of dividing body components which is not based upon anatomical structure alone, may offer a significant new point of view. The following shows the details of the units and the anatomical, physiological and psychological components of each unit.

The five tsang (stores): "What are called the five solid organs store life essence and energy (hsieh and chi) and do not let them leak away; therefore, they are filled but cannot be full."[14]

- *Hsin*—Stores the organ heart, the function of the brain and the psychological function of the mind. It is expressed by the element fire.
- *Kan*—Stores the organ liver, the liver function, the sensory-motor system, and the psychological function of equilibrium and tranquility. The element wood represents it.
- *P'i*—Stores the organ spleen-pancreas, the functions of absorption, digestion, distribution and utilization of nourishment at both the organic and cellular level. The psychological component is temper and intelligence. The element that represents it is earth.
- *Fai*—Stores the organ lung and the respiratory function of gas exchange at both the organic and cellular levels. The psychological component is the willpower and the element metal represents it.
- *Shen*—Stores the organ kidney and the function of the endocrine system such as the functions of the neurohormonal system. The psychological component is the willingness of the person and the element representing it is water.

The six fu (houses): " . . . the six hollow organs transmit and transform matter but do not store it; thus they are full and cannot be filled."[14]

- *Tan*—Houses the gall bladder. The function is to control the circulation of lymphatics and other body fluids such as the fluid in the peritoneum. The psychological and representative elements are the same as its partner kan, which are equilibrium, tranquility, and "wood."
- *Hsiao Ch'ang*—Houses the small intestine, the function of absorption of digestive nutrients from the lumen into the blood stream and the transportation of waste products to the large intestine. The psychological component is the same as hsin, the heart, which is also the mind. Fire is the element that represents it.
- *Wei*—Houses the organ stomach, the function of digestion and the mechanism of muscular contractions. The psychological component is the same as p'i, temper and intelligence, and it is represented by earth.
- *Da-ch'ang*—Houses the organ large intestine. The function is the self-defense mechanism, particularly for cellular response to infection and the immunological system. The psychological component is the same as the fai, willpower, and the element represented by it is metal.
- *Pang-kuang*—Houses the organ urinary bladder and the function is water balance and excretion. It is paired with shen, the kidney, therefore its psychological component is the same: compliance and the element representing it is water.
- *San-chiao*—May be translated as "triple-burner," which represents the three functional zones of the body. The upper governs respiration and cardiovascular circulations, the middle one is for digestion and the lower zone for excretion. This unit is a coordinator of all functions of the body and, like the hsin unit, is represented by fire.

From the above listing, one can see the specific understanding in Chinese medicine that all the organs and functions of the body are closely related to the psyche, and that in the literature, the psychosomatic relationships are well known and well documented.

The Concept of Physiology in Chinese Medicine

There has been much discussion about the need for a Western-trained person to study the formula of "five elements" because it appears to be highly mysterious: yet, at times, its application seems oversimplified. However, if one really wants to understand the trend of thought behind the Oriental approach to medicine, this study is essential. It simply uses the daily events surrounding us to describe the various functions of our body. For instance; the "water" can kill the "fire," the "fire" can melt the "metal"; consequently if the kidney is damaged, it may affect the heart, and the heart trouble will cause damage to the lungs, and so on. Using this simple illustration one can describe the complicated interreaction of the body functions at different times. It

was written in Su-Wen, "The five elements, wood, fire, earth, metal, water, encompass all the phenomena of nature. It is a symbolism that applies itself equally to man."[15]

Because in Chinese medicine the concept of health depends upon the state of equilibrium, to keep perfect equilibrium of one's body is the goal. This calls for the five stores and six houses to be in perfect harmony with one another, and at the same time in harmony with the environment surrounding the person. In other words, the small and large universes are in perfect harmony. Any change in one part of the body or the environment will set off a chain reaction in other parts and thereby disrupt the state of equilibrium. This requires the capacity of the readjusting power within the body to regain its equilibrium. This complicated reaction and counterreaction are illustrated by the law of five elements and using the above mentioned principle.

The Concept of Pathophysiology in Chinese Medicine

In Chinese medical literature the causes of diseases are almost equally divided into six physical aspects and seven emotional factors, or outer and inner insults. The former are the wind, cold, heat, dampness, dryness and fire. The latter are happiness, anger, sorrow, anxiety, sadness, fear and shock. For instance, "The vicious energies of wind and cold attack the upper half of the body, while the vicious energy of dampness attacks the lower half. However, when vicious energies attack the yin meridians, they will cause disease to the bowels; and when they attack the yang meridians, they will cause disease to the meridians themselves . . ."[16]

"Worry and fear may cause harm to the heart; exposing oneself to cold and consumption of cold food may cause harm to the lungs . . ."[16] Credit should be given to the very early recognition of psychosomatic medicine by the Chinese: "in my opinion, only an unskilled physician will confine himself to the physical appearance of his patient, a skilled physician will go one step further and examine the emotions of his patient as well."[4]

The Concept of Maintaining and Promoting Health

Since the definition of good health means the state of equilibrium within one's body and with one's surroundings, the way of maintaining health and promoting health is eventually to keep the balance of all the body functions, the body and the mind, the person and his environment.

Within the body, there are two systems of circulation described in the classical Chinese literature: chi (air) and hsieh (blood). Chi represents the invisible circulation of the vital energy and, therefore, is classified as yang. This energy circulates along definite pathways within definite periods of the day and ceases to circulate when the organism dies. These pathways are called hsieh, according to our present understanding, and include all the visible circulations of the body, such as cardiovascular, lymphatic and even cerebrospinal fluid. Only when these two circulation systems maintain a constant balance, can a person be kept in perfect equilibrium.

In fact, it was detected in the medical literature that the Chinese were fully aware of the circulating nourishment and self-defense mechanism in describing different kinds of chi function. One of them is called yin-chi (nutritional circulations); the other one is called wei-chi (defensive circulation).

"Man receives chi in his food. Chi, entering the stomach is transmitted to the lungs, the five solid and six hollow organs, so that all these may receive chi. The power part of food is nourishing chi, or yin-chi; the less pure part: protecting chi, or wei-chi; yin-chi, being within the meridians and blood vessels, and wei chi outside them."[17]

"Nourishing chi collects fluid and pours it into the vessels changing it into blood in order to nourish the four extremities and to flow into the solid and hollow organs . . . . Only if the vessels are so regulated that there is an uninterrupted circulation of blood can they be strong, vigorous and supple. Thus the reason why the eyes can see, the feet walk, the hand grasp and the skin sweat, because they are all irrigated by blood."[18]

Adapting the above descriptions, we can see that the chi in Chinese literature represents all the invisible functions of the body—the vital energy, the nerve impulses, the automatic control of the mental activities. Hsieh represents the visible circulations, the organs and actually the body itself. In order to maintain health, one must keep equilibrium between the functions and the organs of one's self, and between the mind and the body by keeping in balance one's chi and hsieh.

Maintaining the balance between body and environment can be done through adjustment of the chi and hsieh circulating through the meridians (tracts): "The 12 meridians are externally in

tune with the 12 meridian-like rivers, and internally they are in tune with the five stores and the six houses . . . .

"Therefore, the standards governing the techniques of acupuncture therapy and moxibustion therapy which are aimed at adjusting the energy of meridians can be in harmony with those governing the 12 meridian-like rivers which are aimed at adjusting the flow of water in the rivers."[7]

In other words, in order to keep balance between man and his environment, the meridians are the communication routes. Since meridians are supposed to connect nearly a thousand acupuncture points (skin receptors of acupuncture stimuli) of the body, skin is really the reactor of the body to the surroundings. This does fit into the Western theories of the cutaneous-visceral and the viscerocutaneous reflexes and the referring pain tracts. That it is the relation between cutaneous caresses and contact which stimulates the homeostasis and produces soothing effects.

The Therapeutic Concept in Chinese Medicine

When there is a disruption of the balance of the body function or body and mind, traditional Chinese physicians use either the pharmacological approach—herb medicine—or the physical approach—acupuncture and moxibustion through the meridean system.[19] (A complete text on acupuncture techniques was *Jai Yi Ching* containing 118 chapters.[19])

Preventive Medicine

"To administer medicine for diseases that have already developed and to suppress revolts that have already developed are comparable to the behavior of those persons who begin to dig a well after they have become thirsty, and to those who begin to make their weapons after they have already engaged in battle. Would these actions not be too late?"[20]

"I have heard that in ancient times the people lived to be over a hundred years and yet they remained active and did not become decrepit in their activities, but nowadays people only reach half of that age and yet become decrepit and failing. Is it that mankind is degenerating through the ages and losing his original vigor?"[21]

Chi-Po answered: "In ancient times those people who understood the ways of nature, patterned themselves upon the yin and yang. Modern man drinks wine like water, leads an irregular life, engaging in sexual intercourse while he is drunk thus exhausting his vital energy. They do not know how to preserve their vital force, wasting energy excessively seeking only physical pleasure, all of which is against the rules of nature. For these reasons they reach only half of the hundred years and then they degenerate."[21]

It is interesting to know that, although the dangers of self-indulgence were documented three thousand years ago, modern man continues to ignore those dangers.

This general review should lead the reader to a better understanding of the Chinese concept of medicine.

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(*Huang-Ti Nei Ching* [*The Yellow Emperor's Canon of Medicine*] was originally published in two volumes, in which the Ling-Shu describes the theory and the Su-Wen discusses the practical aspects of acupuncture and moxibustion. Chi-Bai is thought to be Huang-Ti's medical officer. From the geographical names, literary construction and historical allusions, it may be assumed that the *Nei Ching* was published about the end of the Chou dynasty [1121-249 BC] or the beginning of the Chin dynasty [221-207 BC]. The contents are naturally much older. Evidently it is not the work of a single person but a compilation of various writers.)

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Planning Continuing Medical Education Activities

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A review of program development literature in adult education and continuing medical education (CME) indicates the pervasive influence of a single approach to designing instructional activities. An examination of the assumptions of this model indicates several weaknesses. An alternative model is proposed that recognizes the importance and impact of the planners' interaction with representatives of the learner group, institutional colleagues and persons in outside agencies. Results of previous research, experience in planning, observations of the planning processes of others and discussions with expert continuing medical educators show that planning is a dynamic process of suggesting and selecting from many alternatives those instructional activities with the greatest potential for effecting the desired changes in learners. Through a series of deliberations, needs are specified, instructional activities are designed, goals and objectives are stated, and evaluation techniques are selected. CME planners direct the process and constantly focus on the immediate impact on the learners and ultimately on the learners' practice behavior.

PLANNING EFFECTIVE continuing medical education programs is an art and a science. Current emphasis focuses to a great extent on the science-reliable needs assessments, objectives stated behaviorally and outcomes measured by changes in performance. Focusing singly on the science of program development fails to recognize the importance of the human interactions essential to developing learner focused instructional activities. There is no beginning or ending point to planning continuing medical education instructional activities just as there are no temporal boundaries to an individual's learning behaviors. This article blends the art and science of planning into a dynamic program development model focusing on the planner and that planner's concern for the individual physician as a learner.

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The Planning Process

There are no shortcuts to planning effective continuing medical education instructional activities. Planners, however, are not without adequate knowledge resources to use in understanding the program development process. Conceptual tools to guide the process are available in the continuing education literature as well as a few articles in the literature of continuing medical education. While this information suggests a variety of operational strategies it does not adequately describe the hard work of taking vague and esoteric ideas about what ought to make up continuing medical education instructional activities and translating them, through human interactions, into specific learning activities that can effect changes to improve patient care.

The process of planning continuing medical education instructional programs is similar to general processes by which effective programs

for adults in any setting are developed, and to what elementary and secondary education refer to as curriculum development.

For many years successful curriculum development models have been based on the thinking of a generation of theorists from Franklin Bobbitt to Ralph Tyler. The logical operations of this classical model are determining objectives, stating them in appropriate form, devising learning experiences to attain given outcomes and evaluating those experiences.

Program development models presented in adult and continuing education literature illustrate the influence of the logical operations of the classical model on the field of continuing education.[1-3] With the addition of a few operations which describe, assess and involve the client in the planning process these models are basically classical curriculum development statements.

The Classical Planning Model

Two planning models presented in the continuing medical education literature are based on the classical model. The bi-cycle process[4] approaches planning as a problem-solving strategy and includes the basic steps in the classical model. Hutchison's[5] statement on program development combines several credos of adult education with the operations of the classical model to describe a way to plan effective programs for health professionals. Accreditation systems currently employed by a variety of organizations in Medicine include requirements to adhere to most of the operations in the classical curriculum development model.

With these resources planners of continuing medical education activities could acquire information about effective planning strategies. Most planners of continuing medical education programs say that they plan by the "seat of their pants" using no systematic approach.[6] Several reasons for not using available knowledge resources could be suggested, including lack of time, interest or knowledge of resources. Another reason is the inherent problems in the classical model itself and the application of that model to planning in continuing medical education.[7,8]

The classical model assumes that it is possible to predict accurately what the outcomes of an instructional activity will be—behavioral change. In the real world, however, the outcomes of instruction are far too complex and dynamic for behavioral objectives to specify. For many continuing medical education activities the assessment of behavioral outcomes from a single program is inappropriate since the learning that occurs as a result of the instruction is but one input into many information seeking behaviors of the learners. It is the composite of the many experiences that effect behavioral change. In some content areas of continuing medical education it is possible to be precise in specification of outcomes. In others it is not possible or desirable since a consensus in the profession does not exist and could possibly stifle progressive thinking that might lead to innovation and discovery.

A second problem with the behavioral orientation of the classical approach is the assumption that achievement of objectives can be used as the standard for judging program success or failure based on the accumulation of objective evidence. This emphasis fails to distinguish between the application of a standard and making judgments. The application of a standard requires agreement on the defined quantity by which other qualities can be compared. Not all outcomes in continuing medical education programs are amenable to measurement. Even if measurable standards were available the patience and resources of most continuing education providers to measure long-term, readily observable and measurable behavioral change does not exist.

Finally, there is a real danger that planners and instructional faculty do not completely understand the objectives, especially their broad implications in the clinical setting, even when they were instrumental in preparing them. In the classical model objectives are stated very early in the planning process and often overlooked until the evaluation. Too early a statement of objectives obscures other potentially significant learning outcomes that do not become apparent until later because they are seldom anticipated.

The logical flow of activities in the classical model seems a reasonable approach to program development. The procedure of first identifying objectives and then designing instruction is defensible; however, it is not necessarily the most psychologically efficient way to proceed for the planner or the learner the program is designed for.

The Naturalistic Planning Model

Walker[9] proposes a framework that provides an alternative to the classical model which recognizes the planning process as one of human inter-

action. This naturalistic model consists of three elements: platform, deliberation and design. Each element describes a set of constructs that, in practice, have an impact on planning continuing medical education activities.

The Platform for Program Development

The platform is the belief and value system that the planner brings to and uses to guide the program development process. This includes the planner's idea of what health care is and what it ought to be, including his attitudes about continuing education, the learner, and the relationship of both to the improvement of patient care.

Deliberation in Program Planning

Deliberation is that process through which competing ideas for instructional activities are considered, priorities are selected and consequences are projected before decisions are made about what will be included in the program. Deliberation is a natural occurrence in program planning that generates alternative solutions, weighs pros and cons, and considers costs and consequences. It results in choosing not the *right* alternative, for there is no such thing, but the most appropriate one that will result, it is hoped, in an instructional activity providing the participants with a learning experience that they can use to improve their practice.

Program Design

A program's design is the learning activities and the materials-in-use that have been selected to influence the learners' behavior. The focus of all planning for continuing medical education should be on what the program can be expected to do to facilitate positive changes in the learner's knowledge, skills or sensitivities which can be used to improve that person's patient care activities.

Planning continuing medical education programs using the "operations" of the "naturalistic model" includes four basic functions. First the identification of potential program goals. Goals of some magnitude exist for programs even if systematic planning is not carried out. The planning process enables the planner to select particular goals, from a universe of goals, that seem to be appropriate for the program.

The second function defines alternative means for reaching potential goals. Systematic planning necessitates that planners have an array of alternatives to select from in designing effective continuing medical education instructional activities. Too often those of us who plan these programs make decisions based on a very limited knowledge of alternative ways to achieve the same desirable outcomes.

Planners also define the possible consequences of each competing alternative. Common practice is to choose a single activity, implement it and analyze the consequence of that choice without considering other viable options. In continuing medical education we can no longer enjoy the luxury of this procedure. In terms of cost alone (not merely dollars and cents), planners need to be as fully apprised as possible of the probable consequences of programs and activities before acting.

Finally, planners must determine the allocation of resources. As alternatives are considered and deliberation occurs, the resources required to implement each alternative must be considered. Planning, therefore, can and should lead to a more efficient and effective allocation of resources. Systematic planning minimizes haphazard and episodic allocation of resources (funds and personnel) to activities with no real potential for improving professional competence and patient care.

This approach to planning accepts the fact that varying viewpoints about what should be achieved as a result of continuing medical education will emerge. It focuses on the learner and what instructional activities, among many, might reasonably be expected to effect changes in patient care. Objectives become the end product of planning rather than the beginning. The selection of the *right* instructional activity is not required, rather the selection of an appropriate activity from among many results in the program. In the real world of planning continuing medical education these activities are typical. The statement and measurement of behavioral objectives as the beginning and end point of programs is the exception.

A Program Development Model

Most planners of continuing medical education instructional activities recognize that the operations of the classical model must be completed and that the human interactions of the naturalistic model cannot be avoided. Figure 1 depicts a program development model that grows out of data from previous research,[10] conversations with con-

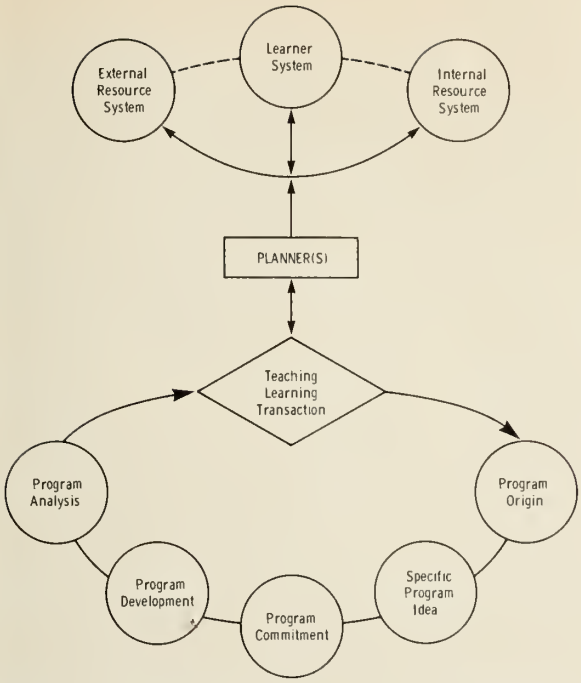

Figure 1.—Program development model. See text for explanation.

tinuing medical education planners, selected literature and experience as a planner of instructional activities for the continuing education of health professionals.

Figure 1 shows the two major dimensions of planning continuing medical education activities—the operations of the classical planning model and the interactions with the resource systems required to complete the planning. The lower part of the model portrays planning functions critical to any planning process. The upper part of the model portrays the major resource systems a planner can recruit and engage in deliberation to plan, implement and evaluate any continuing medical education activity.

Program Origin

The Program Origin includes the variety of sources planners trust as dependable data upon which further planning can be based. These sources typically include the following:

- data from formal needs assessments (audits, peer review and the like);
- requests from current or potential clients;
- guidelines for current or potential research;
- legislative mandates;
- suggestions from academic physicians, and
- data from national, state or local sources describing some aspect of patient care or health behavior.

Specific Program Idea

The cluster labeled Specific Program Idea represents those deliberations planners engage in to narrow the boundaries of the original idea, consider appropriate alternatives, and test how marketable the program is and predict its impact before resources are allocated to the activity. Included are several activities used to specify program ideas:

- testing the idea and alternative approaches with potential clients to explore the extent of interest in the clinical practice setting;
- testing the idea with faculty colleagues or a planning committee to ascertain interest and other sources of information;
- reviewing relevant literature;
- ascertaining if the program fits organizational and institutional purposes, and
- projecting impacts of reasonable alternatives.

Through a series of successive approximations, a Commitment to the Program will be made. When that decision is made, a number of activities may occur rather quickly:

- deciding whether to use internal or external resources for instruction;
- conducting a thorough analysis of the potential client group (who do we think will or should attend), and
- initiating program logistics, such as publicity, arrangements for facilities and contracting for food, printing, mailing and the like.

In the midst of the previous activities, the Course Development process has been underway. This includes the following:

- enlisting learners' representatives to assist in planning;
- assessing the precise educational need;
- selecting and stating priority objectives from competing alternatives;
- designing the teaching and learning transactions to effect the desired learning outcomes;
- selecting appropriate instructional formats;
- choosing or preparing effective materials, and
- selecting and enlisting teaching faculty.

The Teaching-Learning Transaction is the result of all planning and preparation. This is the program but planning is still not complete. In the midst of this planned encounter flexibility must be maintained that will permit mid-course adjustments that make the program most responsive to the learners' educational needs. The planning is complete when the last participant leaves the hall.

Much evaluation is conducted as a postprogram analysis and requires planning the following:

- a determination of methods for judging the success of intended program outcomes;
- development of evaluation instruments;
- determination of what to evaluate including appropriateness of objectives, effectiveness of planning and instruction, and outcomes;
- determination of who will use the evaluation data, and
- conducting, summarizing, and report results.

Learner System

The Learner System incorporates professionals who might be recruited to participate in the learning activity. A credo in adult education encourages the involvement of representatives of the client system in the entire planning and evaluation process.[1,2]

Internal Resource System

The Internal Resource System is composed of the resources available in the sponsoring organization. These include faculty, facilities, instructional media, instructional materials, support staff and other essential human and physical resources.

External System

The External System includes the unlimited resources available to the planner outside the sponsoring organization. Resources can be sought from medical centers, universities, government, professional societies, employers, the public, private enterprise and many others.

Every planner knows the available resource systems and how these resources can contribute to their planning efforts. Each role perspective will have unique expectations and requirements. Planners must project how these expectations will affect the alternative plans under consideration. In many instances no outside resources will be deemed appropriate, consequently leaving total program control to the sponsor.

Summary

There are no shortcuts to planning effective continuing medical education instructional activities. No recipe can be conjured that will consistently produce a fail-safe program in every setting. There are resources to use and planning tasks that must be completed for every program development effort. The planner must be flexible and innovative in linking the resources to the problem, creating alternatives and projecting potential outcomes. This is the action of program development.

The learner and the teaching-learning transaction are the focal point for all planning efforts. Continuing medical education programs will be judged on how well the learner applies what is taught, not on how well objectives were stated, how brilliant the design was or how outstanding the lecturer was. To this end the program development process must not only include the operations of the classical model but must also include a dynamic that focuses on how the programming efforts can contribute to facilitating within the learner self-evaluating and self-correcting behaviors.

The model presented in this paper is descriptive, not prescriptive. There is no place for universal prescriptions in planning continuing medical education activities. Each planner must carefully determine the sequence of resource acquisition and performance of planning tasks, recognizing that his programs accountability is a reciprocal of the excellence exercised in program development.

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The 86th Annual Meeting

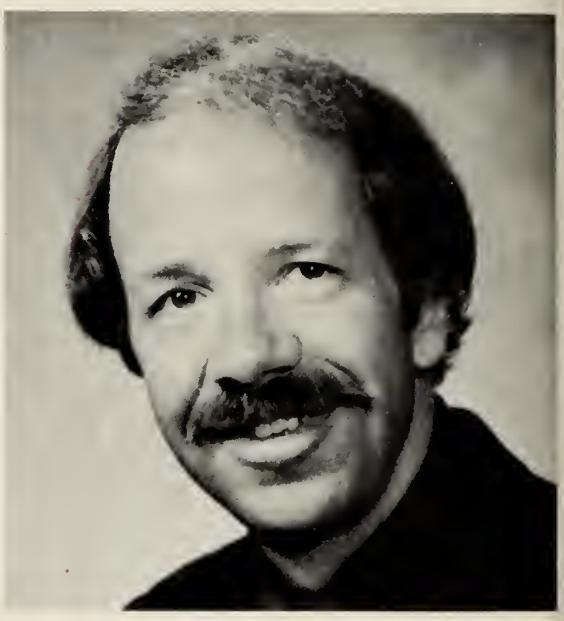
of the

IDAHO MEDICAL ASSOCIATION

July 26-29, 1978

at Idaho's SUN VALLEY

An Invitation to SUN VALLEY



I am very pleased to invite you to attend the 86th annual meeting of the Idaho Medical Association at beautiful Sun Valley.

This meeting offers the satisfaction of a carefully arranged, valid, scientific program, in addition to the exhilaration of high country in the summertime.

There is a unique social program with the Trail Creek Barbecue and a banquet without speeches.

And there is time to enjoy recreational offerings including golf, tennis, swimming, hiking, sightseeing, riding, trapshooting, bowling and more.

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ROY J. ELLSWORTH, MD
President, Idaho Medical Association

86th Annual Meeting
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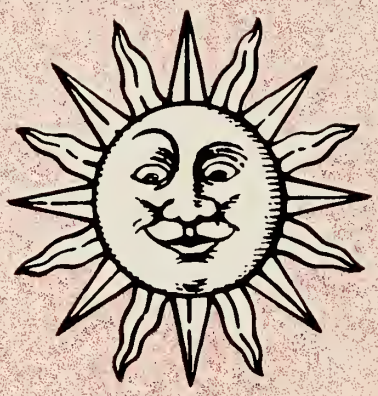

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IDAHO MEDICAL ASSOCIATION
86th Annual Meeting

Wednesday, July 26, 1978

8:30 a.m.-5:00 p.m. House of Delegates

Thursday, July 27, 1978

8:15 a.m. Welcome

ROY J. ELLSWORTH, MD
President, Idaho Medical Association

Introduction

DAVID K. MERRICK, MD
Program Chairman

8:30 a.m. Computers in Medicine: Boon or Boondoggle?

JOHN H. GREIST, MD
Associate Professor of Psychiatry, University of Wisconsin Medical Center

9:00 a.m. Computer Consultation: Has the Computer Replaced the Consultation?

HOWARD L. BLEICH, MD
Associate Professor of Medicine, Harvard Medical School

10:15 a.m. Computer Programming: How to Give a Computer the MUMPS

JUDITH R. FAULKNER, MS
President, Human Services Computing, Inc., Nashotah, Wisconsin

A. NEIL PAPPALLARDO, MS
President, Meditech, Inc., Cambridge, Massachusetts

11:00 a.m. Computer Interviewing: Have You Had a Pain in Your §#%&!?

WARNER V. SLACK, MD
Associate Professor of Medicine, Harvard Medical School

11:45 a.m. Business Aspects of Medical Computing: More for Your Money

A. NEIL PAPPALLARDO, MS
JUDITH R. FAULKNER, MS

12:30 p.m. Adjourn

Friday, July 28, 1978

8:15 a.m. Introduction

8:30 a.m. Man—Machine Problems

9:15 a.m. Computer Hardware: "Black Boxes"

A. NEIL PAPPALLARDO, MS
HOWARD L. BLEICH, MD

10:15 a.m. Other Applications

HOWARD L. BLEICH, MD
JUDITH R. FAULKNER, MS

11:00 a.m. Panel Discussion

JOHN H. GREIST, MD, *Moderator*

11:45 a.m. Household Computers: A Lovable Helpmate?

WARNER V. SLACK, MD

Saturday, July 29, 1978

8:30 a.m.-1:30 p.m. Closing Session, House of Delegates

For information, contact:

IDAHO MEDICAL ASSOCIATION
P.O. Box 2668
Boise, Idaho 83701
Telephone: (208) 344-7888

AUTHOR INDEX

Adler, Martin E., Sacramento, CA.....(Feb) 165
Ahmad, Aftab, Portland, OR.....(May) 377
Anders, Thomas F., Stanford, CA.....(Jun) 477
Anderson, Bruce C., Portland, OR.....(Mar) 203
Antoniskis, Andris, Portland, OR.....(Mar) 203
Avina, Robert L., La Jolla, CA.....(Apr) 366
Awad, Essam A., Minneapolis.....(Jan) 68

Babb, Richard A., Palo Alto, CA.....(Mar) 244
Barraff, Larry J., Los Angeles.....(Feb) 159
Basden, Millie, Fresno, CA.....(Feb) 101
Beall, Gildon N., Los Angeles.....(Mar) 240
Beck, Clyde H. Jr., La Jolla, CA.....(Apr) 343
Bilitch, Michael, Los Angeles.....(Mar) 248
Birnbaum, William, Long Beach, CA.....(Jan) 6
Bradley, William, San Francisco.....(Jun) 512
Bresnahan, Gerald F., Inglewood, CA.....(Jan) 72
Bruyn, Henry B., San Francisco.....(Feb) 178
Butler, Lewis H., San Francisco.....(Jun) 512

Cantor, David S., Sacramento, CA.....(Apr) 347
Carmel, Ralph, Los Angeles.....(Apr) 294
Carskadon, Mary A., Stanford, CA.....(Jun) 477
Cello, John P., San Francisco.....(May) 419
Chapman, Richard D., Portland, OR.....(May) 377
Chesne, Robert B., Inglewood, CA.....(Jan) 72
Chin, James, Berkeley, CA.....(Mar) 195
Chow, Anthony W., Torrance, CA.....(Mar) 189
Chrispens, Jere E., Loma Linda, CA.....(Jan) 85
Ciraulo, David A., Inglewood, CA.....(Jan) 72
Clark, Albert G., San Francisco.....(Jun) 548
Comfort, Alex, Santa Barbara, CA.....(Mar) 257
Cooper, Thomas P., Seattle.....(Feb) 185
Cordes, Sam M., University Park, PA.....(Jan) 75
Corrin, Adaline, San Diego.....(Feb) 127
Crocker, Susan, San Francisco.....(Feb) 178

Daskalakis, Michael K., Anaheim, CA.....(Apr) 345
Davidson, Howard, San Francisco.....(Jan) 64
Davis, Charles, Los Angeles.....(Mar) 246
Demanes, D. Jeffrey, Los Angeles.....(Jan) 71
Dement, William C., Stanford, CA.....(Jun) 477
Dewar, C. Richard, Sacramento, CA.....(Apr) 370
Don, Hillary F., San Francisco.....(Apr) 318
Drasin, Harry, San Francisco.....(Feb) 106
Dreyfus, Pierre M., Davis, CA.....(Jun) 499

Edmiston, W. Allan, Los Angeles.....(Mar) 248
Eickhoff, Theodore C., Denver.....(Mar) 236
Eliastam, Michael, Stanford, CA.....(Jun) 547
Emmons, Richard W., Berkeley, CA.....(Feb) 159

Fairshter, Ronald D., Orange, CA.....(Jan) 56
Felton, Jean Spencer, Long Beach, CA.....(Mar) 266
Fitzgerald, Faith, Ann Arbor, MI.....(Mar) 223
Flaherty, Walter T., Tustin, CA.....(Apr) 351
Ford, James H., Downey, CA.....(Mar) 255
Fox, E. R. W., Coeur d'Alene, ID.....(Apr) 352
Francis, Charles K., Los Angeles.....(Jan) 1
Frank, Richard D., Vallejo, CA.....(Feb) 170
Frick, Oscar L., San Francisco.....(May) 437
Friedman, William, San Diego.....(Mar) 212
Fripp, Elaine, San Francisco.....(Apr) 318

Gardner, Ernest D., Davis, CA.....(Jun) 499
Gilbert, David N., Portland, OR.....(Mar) 203
Gill, Mark A., Los Angeles.....(Mar) 246
Gitnick, Gary L., Los Angeles.....(Feb) 117
Glomset, John A., Seattle.....(Jan) 55
Gluck, Louis, San Diego.....(Mar) 212
Gough, Harrison G., Berkeley, CA.....(Jan) 81
Granoff, Dan M., Fresno, CA.....(Feb) 101
Greenberg, Bernard R., Davis, CA.....(Jan) 71
Griswold, William, La Jolla, CA.....(Jun) 543
Grundy, Scott M., San Diego.....(Jan) 13
Guilleminault, Christian, Stanford, CA.....(Jun) 477
Gunn, Robert, Atlanta.....(Feb) 159
Guze, Lucien B., Los Angeles.....(Mar) 189

Haburchak, David R., Fort Sam Houston, TX.(Jan) 64
Hadley, G. Gordon, Loma Linda, CA.....(Jan) 85
Hafkin, Barry, Atlanta.....(Feb) 159
Hall, Wallace B., Berkeley, CA.....(Jan) 81
Ham, Joe N., Orange, CA.....(May) 450
Hamburger, Robert N., San Diego.....(May) 408
Harvey, Kim, Stanford, CA.....(Jun) 477
Herbert, Victor, Bronx, NY.....(Apr) 338
Hershman, Jerome M., Los Angeles.....(Mar) 240
Hess, George H.,
Carson City, NV.....(Apr) 282, (Jun) 547
Heymann, Michael A., San Francisco.....(Mar) 238
Higgins, Charles, San Diego....(Feb) 127, (Mar) 212
Hinds, M. Ward, Olympia, WA.....(Feb) 169
Hoefs, John C., Los Angeles.....(Apr) 305
Hoff, Julian T., San Francisco.....(Feb) 112
Hopewell, Philip C., San Francisco.....(May) 435
Hultgren, Herbert N., Palo Alto, CA.....(Jun) 536
Hurwitz, Alfred L., San Francisco.....(Jan) 89

Imperato, Thomas J., Sacramento, CA.....(Apr) 347
Incaudo, Gary I., San Diego.....(May) 408

Jackson, Joanne M., Portland, OR.....(Mar) 203
James, Walter S. III, Palo Alto, CA.....(Jan) 60
Johnston, D. Gordon, Los Angeles.....(May) 390
Johnston, William, San Diego.....(Jun) 543
Jones, William A., Seattle.....(Feb) 185
Jonsen, Albert R., San Francisco.(Apr) 318, (Jun) 512
Jordan, George, Sacramento, CA.....(Feb) 165
Juels, Charles, Norfolk, VA.....(Mar) 195

Kahler, Stephen, San Diego.....(May) 408
Kaneko, Jeanne, Los Angeles.....(Mar) 246
Kaplan, Allen M., Phoenix, AZ.....(Apr) 279
Kark, Pieter, Los Angeles.....(Jun) 537
Kay, Jerome, Los Angeles.....(Mar) 248
Keene, Barry, Sacramento, CA.....(Apr) 318
Kennedy, Donald, Rockville, MD.....(Mar) 254
Kern, Jack W., Los Angeles.....(Mar) 246
Kerr, William B., San Francisco.....(Jun) 512
Ketchum, James S., Sherman Oaks, CA.....(May) 450
Kieraldo, John H., Palo Alto, CA.....(Mar) 244
Kirkpatrick, Stanley E., San Diego.....(Feb) 127
Kiviat, Mark D., Seattle.....(Feb) 185
Klutch, Murray, San Francisco.....(Apr) 329
Krevans, Julius R., San Francisco.....(Apr) 318

Lackner, Jerome, Sacramento, CA.....(Apr) 318
Laiken, Stuart, La Jolla, CA.....(Apr) 343
Laman, Paul David, Stanford, CA.....(Jan) 26
Lau, Francis Y. K., Los Angeles.....(Mar) 248
Lavery, Kathleen R., San Francisco.....(Apr) 318
Lee, Philip R., San Francisco.....(Jun) 512
Levine, Gerald A., Los Angeles.....(Mar) 240
Lieberman, James S., Davis, CA.....(Jun) 499
Longhurst, William L., Phoenix, AZ.....(Apr) 279
Lubin, Craig, San Francisco.....(Jun) 512

Maletzky, Barry M., Portland, OR.....(Jun) 488
Manning, Phil R., Los Angeles.....(Mar) 260
McKeon, James, Los Angeles.....(Mar) 246
Mellon, Michael, San Diego.....(May) 408
Melo, Joao Q., Portland, OR.....(May) 377
Mendoza, Stanley, La Jolla, CA.....(Jun) 543
Menn, Stuart J., San Diego.....(Jan) 60
Merritt, T. Allen, San Diego.....(Mar) 212
Merten, David F., Durham, NC.....(Apr) 370
Meyerowitz, Basil R., San Mateo, CA.....(Jun) 549
Midgley, Robert C., Sacramento, CA.....(Apr) 347
Mills, Don Harper, Los Angeles.....(Apr) 339
Mills, William J., Jr., Anchorage, AK.....(Jun) 471
Minuth, Andre N., Fresno, CA.....(May) 452
Miser, James S., Columbus, OH.....(May) 440
Morrison, Florence R., Berkeley, CA.....(Mar) 195
Morrison, James R., La Mesa, CA.....(Jun) 482
Moser, Kenneth M., San Diego.....(Jan) 60
Mosley, James W., Los Angeles.....(Apr) 305

Nadas, Alexander S., Boston.....(Feb) 157
Nelsen, Alan C., Kailua, HI.....(May) 453
Newman, John H., Denver.....(May) 399
Nichols, Steven, San Diego.....(Jun) 543
Nusser, Richard A., Oakland, CA.....(May) 443
Nyhan, William L., San Diego..(Feb) 127, (Mar) 212, (May) 408

Oill, Phyllis A., Torrance, CA.....(Mar) 189
Oshtory, Meherji, Davis, CA.....(Jun) 499
Overturf, Gary D., Los Angeles.(Feb) 159, (Mar) 195
Owen, Robert L., San Francisco.....(Jan) 89

Pakes, Gary E., Culver City, CA.....(Feb) 171
Palmer, Edward, Lake Oswego, OR.....(Apr) 351
Parker, Robert G., Los Angeles.....(Jan) 71
Pennington, Floyd C., Ann Arbor, MI.....(Jun) 558
Peters, Robert L., Los Angeles.....(Apr) 305
Petty, Thomas L., Denver.....(May) 399
Pickersgill, Judith, Stanford, CA.....(Jan) 26
Poirier, Tommy, Sacramento, CA.....(Apr) 347
Propst, Michael T., Anchorage, AK.....(Jun) 471

Quinn, Bernice, Vallejo, CA.....(Apr) 354

Raffin, Thomas A., Stanford, CA.....(Jan) 26
Randall, Donald L., Phoenix, AZ.....(Apr) 279
Redeker, Allan G., Los Angeles.....(Apr) 305
Reynolds, Michael D., Orange, CA.....(Apr) 285
Reynolds, Ralph D., Travis Air Force Base, CA.....(Jan) 71
Reynolds, Telfer B., Los Angeles.....(Apr) 305
Rickles, David J., Los Angeles.....(Jan) 71
Riker, Jeffrey, Long Beach, CA.....(Jun) 542
Roback, Michael David, Los Angeles.....(Jun) 549
Roberto, Ronald R., Berkeley, CA.....(Mar) 189, 195
Robertson, William O., Seattle.....(May) 440
Robin, Eugene D., Stanford, CA.....(Jan) 26
Robinson, William S., Stanford, CA.....(Feb) 153
Rockwell, Richard, Fresno, CA.....(Feb) 101
Rodgers, David Leigh, San Francisco.....(Feb) 171
Roe, Benson R., San Francisco.....(Apr) 318
Rogers, Donald R., Anchorage, AK.....(Jun) 471
Rogers, William F., Los Angeles.....(Jan) 6
Rosinski, Edwin F., San Francisco.....(Apr) 370
Rudin, Edward, Sacramento, CA.....(May) 459

Sadler, H. Harrison, San Francisco.....(Apr) 318
Salmon, Pierre, Hillsborough, CA.....(Apr) 353
Saylam, Argun, Portland, OR.....(May) 377
Schneiderman, Lawrence J., La Jolla, CA....(Apr) 366
Schou, Mogens, Risskov, Denmark.....(Jun) 535
Schroeder, Steven A., San Francisco.....(Jun) 512
Schwartz, Harold, Lakewood, CA.(Feb) 174, (Jun) 550
Schweigert, Byron, Long Beach, CA.....(Jun) 542
Seidenverg, Norman F., Vallejo, CA.....(Apr) 354
Shapiro, Stephen R., Sacramento, CA.....(Apr) 370
Shaub, Michael S., Los Angeles.....(Jan) 6
Shirley, James H., Travis Air Force Base, CA.(Jan) 71
Shore, James H., Portland, OR..(Mar) 207, (Jun) 488
Sidhu, Dip S., Fontana, CA.....(Jun) 539
Silk, Arthur D., Garden Grove, CA.....(Jan) 73
Simmons, F. Blair, Stanford, CA.....(Jun) 477
Simon, Lawrence M., Stanford, CA.....(Jan) 26
Simons, David G., Huntington Beach, CA...(Jan) 69
Smith, David E., San Francisco.....(May) 449
Smith, Lloyd H., Jr., San Francisco....(Feb) 133, 151
Solters, John, San Francisco.....(Apr) 318
Spetzler, Robert, San Francisco.....(Feb) 112
Sproul, Gordon, San Diego.....(Apr) 291
Starr, Albert, Portland, OR.....(May) 377
Steinberg, Evan, Los Angeles.....(Feb) 159
St. Geme, Joseph W., Jr., Torrance, CA....(May) 382
Swanson, Margo, Long Beach, CA.....(Jun) 542

Tan, Kong Meng, Richmond, CA.....(Jun) 548
Tarkoff, Mitchell P., Oakland, CA.....(May) 443
Thadepalli, Haragopal, Los Angeles.....(Jan) 1
Theodore, James, Stanford, CA.....(Jan) 26
Thoeni, Ruedi, San Francisco.....(May) 419
Timms, Richard M., La Jolla, CA.....(Apr) 343
Tong, Myron J., Los Angeles.....(Apr) 305
Trummer, Max J., San Diego.....(Jan) 74
Tsuei, Julia J., Honolulu.....(Jun) 551

Ungerleider, J. T., Los Angeles.....(Feb) 173

Valentine, William N., Los Angeles.....(Jan) 35
Van Volkinburg, Earl J., Portland, OR.....(Mar) 203
Vijayan, Nazhiyath, Davis, CA.....(Jun) 499
Vincent, Keith E., Vallejo, CA.....(Apr) 354

Walpin, Lionel A., Beverly Hills, CA.....(May) 451
Walter, Robert M., Jr., Sacramento, CA.....(Feb) 165
Warrens, Albert E., Chico, CA.....(Mar) 256
Wehrle, Paul F., Los Angeles.....(Feb) 159
Weinberger, Laurence, Ventura, CA.....(Jan) 68
Wetrich, Raymond M., Fontana, CA.....(Jun) 539
Widmeyer, Mary, Stanford, CA.....(Feb) 170
Williams, Donald E., Los Angeles.....(Mar) 240
Wilson, Robert L., Torrance, CA.....(Jan) 6
Wilson, Rodman, Anchorage, AK.....(Jun) 471
Winestock, David, San Francisco.....(Feb) 112
Wiseman, L. Ward, Anaheim, CA.....(Feb) 172
Wood, James A., Portland, CA.....(May) 377
Woods, Ward W., San Diego.....(Jan) 9

Yassinger, Sidney, Sacramento, CA.....(Apr) 347
Yokoyama, Taro, Los Angeles.....(Mar) 248

Zimmerman, Rick, San Francisco.....(May) 459
Zimmerman, William R., Inglewood, CA....(Jan) 72

IN MEMORIAM

Bailey, William Ellery, Oct 25, 1977 (Jan) 96
Baker, Thomas, Mar 10, 1978 (May) 469
Ball, Dexter R., Jan 4, 1978 (Mar) 277
Barmore, Merrill G., Feb 14, 1978 (May) 469
Bennett, DeWitt Clinton, Jr., Aug 26, 1977 (Mar) 277
Bermudez, Diego, Oct 30, 1977 (Jan) 96
Beukema, John R., Feb 7, 1978 (May) 469
Blanche, Donald W., Oct 7, 1977 (Mar) 277
Bobell, Walter M., Mar 4, 1978 (May) 469
Bonfiglio, Vincent, Sep 9, 1977 (Jan) 96
Brandes, Leo, Nov 24, 1977 (Mar) 277
Brewer, A. Frank, Oct 23, 1977 (Jan) 96
Buchbinder, Egon, Oct 23, 1977 (Jan) 96
Burrows, Ernest George, Mar 1, 1978 (May) 469
Burwell, Lorus C., Jun 15, 1977 (Jan) 96
Bushnell, John W., Dec 2, 1977 (Jan) 96

Castles, Charles C., Sr., Sep 13, 1977 (Jan) 96
Chalmers, Nate, Feb 3, 1978 (May) 469
Cleary, Frank W., Feb 1, 1978 (May) 469
Cohen, Peter, Dec 20, 1977 (Mar) 277
Cohen, William P., Mar 18, 1978 (May) 469
Cole, Leon Rykoff, May 7, 1977 (Mar) 277
Conkling, Charles M., Mar 10, 1977 (Jan) 96
Corbin, Damon Elliott, Feb 22, 1978 (May) 469
Crahan, Marcus Esketh, Jan 11, 1978 (Apr) 376

Davis, Gerald E., Jan 8, 1978 (Mar) 277
DeWeese, Roger Erie, Jr., Dec 3, 1977 (Mar) 277

Erlwein, John F., Jan 5, 1978 (May) 469

Ferguson, Ralph A., Aug 29, 1977 (Mar) 277
Ferguson, Thomas A., Jan 19, 1978 (Apr) 376
Firestone, Fred, Nov 10, 1977 (Jan) 96
Fung, George Dern, Jan 13, 1978 (Apr) 376

Gairdner, Thomas M., Sep 12, 1977 (Mar) 277
Galbraith, Harold, Nov 13, 1977 (Jan) 96
Gardner, Ernest D., Feb 21, 1978 (May) 469
Gocke, John A., Nov 1977 (Mar) 277
Gonzalez, Dario P., Nov 6, 1977 (Mar) 277
Goodfellow, Jack, Feb 23, 1978 (May) 469
Goss, Donald A., Nov 4, 1977 (Jan) 96
Green, John Winston, Jan 19, 1978 (Apr) 376
Greganti, Frank Paul, Nov 8, 1977 (Mar) 277
Gregorius, H. Harvey, Dec 28, 1977 (Mar) 277

Hall, William W., Jan 6, 1978 (Mar) 277
Hanson, Wayne Pierre, Jan 21, 1978 (Apr) 376
Hardesty, John Thomas, Feb 25, 1978 (May) 469
Harrington, John T., Nov 3, 1977 (Jan) 96
Hicks, Avery M., Mar 1, 1978 (May) 469
Horn, Paula M., Oct 4, 1977 (Jan) 96
Hubenka, Albin H., Nov 8, 1977 (Jan) 96
Husser, George D., Dec 27, 1977 (Mar) 277
Hutton, Edward L., Jan 25, 1978 (Apr) 376

Irvine, Richard B., Jun 10, 1977 (Jan) 96

Johnston, S. Theron, Nov 24, 1977 (Mar) 277

Kazmi, Syed, Dec 13, 1977 (Mar) 277
Kelley, Donald T., Nov 22, 1977 (Jan) 96
Kelly, Francis A., Jan 28, 1978 (May) 469
Kieraldo, John Henry, Jr., Oct 27, 1977 (Jan) 96
Kirby, John M., Dec 12, 1977 (Mar) 278
Kistler, Lewis Maxwell, Aug 31, 1977 (Mar) 278
Kroll, Frederick Walter, Dec 15, 1977 (Mar) 278

Ladd, Ervin E., Oct 27, 1977 (Apr) 376
Leach, Charles Wendell, Feb 20, 1978 (May) 469
Leake, Chauncey D., Jan 11, 1978 (Apr) 376
Lee, Daulton Bradley, Aug 5, 1977 (Mar) 278
Levinthal, Daniel, Feb 20, 1978 (May) 469
Lipsett, Edward M., Mar 8, 1978 (May) 469
Loebl, Katherine Maria, Aug 1, 1977 (Apr) 376
Lomas, Max I., Oct 17, 1977 (Jan) 97

MacCracken, Frank Earle, Feb 3, 1978 (Apr) 376
Marinoff, Raymond George, Nov 10, 1977 (Jan) 97
Marsey, Charles F., Jan 3, 1978 (Apr) 376
Maynard, Merlin Trevor-Roper, Feb 5, 1978 (May) 470
McBride, Elizabeth J., Feb 9, 1978 (May) 470
McCracken, Jacob H., Sep 19, 1977 (Mar) 278
McKinnon, Donald A., Feb 2, 1978 (May) 470
McLaughlin, Richard F., Sr., Jan 28, 1978 (Apr) 376
Miller, Frederick J., Feb 12, 1978 (May) 470
Mohun, Charles C., Dec 2, 1977 (Mar) 278
Monahan, John R., May 30, 1977 (Jan) 97
Montanus, John J., Jan 12, 1978 (Apr) 376
Moody, E. Earl, Oct 24, 1977 (Mar) 278
Moore, Charles C., Jan 17, 1978 (Apr) 376
Mulligan, Harold R., Mar 8, 1977 (Mar) 278
Musser, Leo Pratt, Jan 10, 1978 (Apr) 376

Naegeli, Arnold E., Mar 13, 1977 (Jan) 97

Osborne, Clyde J., Mar 7, 1978 (May) 470

Petrilli, Alexander, Jun 11, 1977 (Apr) 376
Pies, Morris, Jun 29, 1977 (Mar) 278
Pulford, DeLos Schuyler, Oct 26, 1977 (Jan) 97

Rarick, Ivan H., Sr., Dec 11, 1977 (Mar) 278
Rose, Jack Morton, Nov 8, 1977 (Jan) 97
Rosser, Bernard Howard, Jan 1, 1978 (May) 470
Rottschafer, Gerald, Dec 18, 1977 (Mar) 278
Rubin, Arthur M., Sep 17, 1977 (May) 470
Ruetman, Henn M., Oct 21, 1977 (Jan) 97
Ruschin, Louis John, Jan 9, 1978 (Mar) 278

Sandor, Andrew A., Nov 19, 1977 (Jan) 97
Sargent, Willard S., Nov 8, 1977 (Jan) 97
Saunders, Joseph Carver, Oct 1, 1977 (May) 470
Schumacher, Irwin C., Nov 26, 1977 (Mar) 278
Schwind, Justin V., May 17, 1977 (Apr) 376
Shultz, Ellwood, Oct 22, 1977 (Mar) 278
Sprong, David H., Jr., Jan 9, 1978 (Mar) 278
Sullivan, Francis J., Mar 28, 1978 (May) 470
Syman, Leo W., Mar 1, 1977 (Mar) 278
Szekely, Joseph L., Jul 25, 1977 (May) 470

Taubert, Ralph T., Dec 30, 1977 (Mar) 278
Thomsen, Frederick H., Jul 8, 1977 (Apr) 376
Touriel, Elie Louis, Oct 6, 1977 (Apr) 376

VonKomaromy, Geza Georg, Nov 1, 1977 (Jan) 97

Walkin, Frank, Nov 16, 1977 (May) 470
Weil, Walter Joseph, Nov 27, 1977 (May) 470
Whitelock, Thomas Sidney, Jr., Dec 2, 1977 (Jan) 97
Willoughby, Glenn Edward, Feb 26, 1978 (May) 470
Wilson, Byron Kent, Dec 30, 1977 (Mar) 278
Wilson, Leland B., Oct 17, 1977 (Jan) 97

Zeligs, Meyer A., Mar 20, 1978 (May) 470

SUBJECT INDEX

A

Abortion Crisis, The—A Countervailing View (Correspondence), James H. Ford.....(Mar) 255
Abraham Lincoln and Cardiac Decompensation—A Preliminary Report (Medicine in American History), Harold Schwartz.....(Feb) 174
Correspondence, Walter T. Flaherty.....(Apr) 351
Reply, Harold Schwartz.....(Jun) 550
Abuse of Blood Components, see *Blood Transfusion*
[Accidental] Poisoning, see *Ipecac*
Acute Renal Failure Associated with Hemodialysis and Hypophosphatemia, Stuart Laiken, Clyde H. Beck Jr., Richard M. Timms.....(Apr) 343
Acute Suppurative Thyroiditis—Diagnostic, Metabolic and Therapeutic Observations, Martin E. Adler, George Jordan, Robert M. Walter, Jr.....(Feb) 165
Addicts, Endocarditis in, see *Diagnostic Clues*
Adult Respiratory Distress Syndrome, see *Legionnaires Disease*
Adult Respiratory Distress Syndrome (Medical Progress), Thomas L. Petty, John H. Newman.(May) 399
Editorial, Philip C. Hopewell.....(May) 435
Aggeler Lecture, see *Hereditary Spherocytosis*
Ailing Health Care System, The (Medical Staff Conference), Discussants: Philip R. Lee, William Bradley, Steven A. Schroeder, Craig Lubin, Albert R. Jonsen, William B. Kerr, Lewis H. Butler.....(Jun) 512
Alternative to Amputation, see *Femoral Tibial Bypass*
Amendments, see *Proposed Constitutional*
[Amphetamines], see *FDA—The 11th Myth*
Ampicillin-Resistant Hemophilus influenzae—Emergence in California's Central Valley, Dan M. Granoff, Millie Basden, Richard Rockwell.(Feb) 101
Amputation, Alternative to, see *Femoral Tibial Bypass*
Anastomosis, see *Correction*
Anemias, see *Diagnosing Megaloblastic*
Anemias, see *Laboratory Diagnosis of Megaloblastic*
Anesthesiology, see *Epitomes*
Aneurysm, Apical, see *Ventricular Tachycardia*
Anorectal Lesions and Syphilitic Hepatitis, David R. Haburchak, Howard Davidson.....(Jan) 64
Antibiotics, see *Outpatient Self-Administration*
Antibiotics, Parenteral, see *Feasibility of Outpatient Self-administration*
Approach to the Treatment of Asthma, An (UC, San Diego, and UC Medical Center, San Diego, Pediatric Conference), Participants: Michael Mellon, Gary I. Incaudo, Stephen Kahler, Robert N. Hamburger, William L. Nyhan.....(May) 408
Editorial, Oscar L. Frick.....(May) 437
Area Health Education Center, see *Central San Joaquin*
Art [of Medicine], see *Science and*
Arteriosus, see *Patent Ductus*

Articles To Read in Other Journals.....(Jan) 92
[Asbestos Related Disease], see *Mesothelioma*
Assault Upon the Professions, The (Editorial) .....(Jun) 534
Assistants, see *Health Screening and Role of Nurse*
Asthma, see *Approach to Treatment*
Asthma, see *Management*
Ataxia, see *Cerebellar*
Ataxia, see *Modern View of*
[Atherosclerosis], see *Cholesterol Metabolism*
[Audit, Medical], see *Monumental Squeak*
[Australia Antigen], see *Viral Hepatitis*
Avicenna Revisited [Iranian Medical School] (Editorial), Lloyd H. Smith, Jr.....(Feb) 151

B

Biological Perspective of Slow Virus Infection and Chronic Disease, see *Seminars in Virology*
Blood Components, see *Blood Transfusion*
Blood Transfusion: Use and Abuse of Blood Components, D. Gordon Johnston.....(May) 390

Book Reviews:

Acupuncture Therapy—2nd Ed., *Tan et al*...(Jan) 93
Blood Gases in Clinical Practice, *Lapuerta*...(May) 467
Calcium, Phosphate and Magnesium Metabolism, *Nordin* .....(Apr) 374
Clinical Orthopaedic Examination, *McRae*...(Jan) 95
Clinical Radiobiology, *Duncan & Nias*.....(Apr) 375
Current Concepts in Radiology—Vol. 3, *Potchen* .....(Mar) 276
Diagnostic Bronchoscopy — An Introduction — 3rd Ed., *Stradling*.....(Mar) 275
Elements of Psychotherapy, Enelow.....(May) 467
Epidemiology and Community Health in Warm Climate Countries, *Cruickshank et al*.....(Apr) 373
General Ophthalmology—8th Ed., *Vaughan & Asbury* .....(May) 467
Hand, The—Diagnosis and Indications, *Lister*.(Jan) 94
Handbook of Obstetrics & Gynecology—6th Ed., *Benson* .....(Jan) 94
Heredity Factor, The—Genes, Chromosomes, and You, *Nyhan & Edelson*.....(Jan) 93
Interpretation of Biochemical Multitest Profiles, *Wolf* .....(Apr) 375
Legal Aspects of Medical Practice—2nd Ed., *Knight* .....(Jan) 93
Microvascular Reconstructive Surgery, *O'Brien* .....(Jan) 94
Motor Disorders of the Esophagus, *Henderson* .....(Mar) 275
Office Gynecology, *Glass*.....(Apr) 373
Paediatric Haematology, *Willoughby*.....(Apr) 374
Recent Advances in Dermatology—No. 4, *Rook* .....(Jan) 94
Renal and Electrolyte Disorders, *Schrier*....(Mar) 275
Pathology and Surgery of the Veins of the Lower Limb—2nd Ed., *Dodd & Cockett*.....(Apr) 373
Recent Advances in Obstetrics and Gynaecology—No. 12, *Stalworthy & Bourne*.....(Apr) 375
Textbook of Epilepsy, *Laidlaw & Richens*...(Mar) 276
Textbook of Physiology and Biochemistry—9th Ed., *Bell et al*.....(Mar) 276

[Bowel], see Crohn Disease
Briquet Syndrome, see *Management*

C

California, see *Medical School Graduates*
California, see *Meningococcal Disease*
California, Medicolegal Considerations, see *Health Screening*
[California Hospital Association], see *Medical Insurance Feasibility Study*

California Medical Association:
Proposed Constitutional Amendments.....(Jan) 98

[California Medical Association], see *Medical Insurance Feasibility Study*
California's Central Valley, see *Ampicillin-Resistant Hemophilus influenzae*
California's Natural Death Act (Medical Staff Conference), Moderator: H. Harrison Sadler; Participants: Julius R. Krevans, Benson R. Roe, Barry Keene, Albert R. Jonsen, John Solters, Kathleen R. Lavery, Elaine Fripp, Hillary F. Don, Jerome Lackner .....(Apr) 318
Appendix: Survey Results After One Year's Experience, Murray Klutch.....(Apr) 329
Cancer, see *Survival in Lung*
Carcinoma, Recurrent Colon, see *Graves Hyperthyroidism*
Cardiac Catheterization, see *Outpatient*
Cardiac Decompensation, see *Abraham Lincoln and*
Cardiopulmonary Resuscitation in Rural Community Hospitals, George H. Hess.....(Apr) 282
Correspondence, Michael Eliastam.....(Jun) 547
Reply, George H. Hess.....(Jun) 547
Catheterization, Cardiac, see *Outpatient*
Central San Joaquin Valley Area Health Education Center, The (Medical Education), Edwin F. Rosinski.....(Apr) 370
Cerebellar Ataxia: Anatomical, Physiological and Clinical Implications (UC, Davis, and Sacramento Medical Center) (Specialty Conference), Participants: Pierre M. Dreyfus, Meherji Oshtory, Ernest D. Gardner, James S. Lieberman, Nashiyath Vijayan.....(Jun) 499
Editorial, Pieter Kark.....(Jun) 537
Children, see *St. Louis Encephalitis*
Children, see *Respiration During Sleep*
Cholesterol Metabolism in Man (Medical Progress), Scott M. Grundy.....(Jan) 13
Editorial, John A. Glomset.....(Jan) 55
Chronic Disease, see *Seminars in Virology*
Chronic Hepatitis B (USC School of Medicine and John Wesley County Hospital, Los Angeles, Interdepartmental Conference), Participants: John C. Hoefs, Robert L. Peters, Allan G. Redeker, Myron J. Tong, James W. Mosley, Telfer B. Reynolds.....(Apr) 305
Editorial, James L. Boyer.....(Apr) 340
Chronic Hepatitis B Infection, see *Prognostic*
Cirrhosis Due to Hypervitaminosis A, Richard E. Babb, John H. Kieraldo.....(Mar) 244
Clinical Diagnosis of Psychogenic Rheumatism, Michael D. Reynolds.....(Apr) 285
Correspondence, Michael D. Roback.....(Jun) 549
Climbing, see *Risks of*
Clinical Medicine, Important Advances in, see *Epitomes*
Colon Carcinoma, see *Graves Hyperthyroidism*
Colonoscopic Polypectomy, see *Retroperitoneal Emphysema*

Commentary:
Geriatrics—The Missing Discipline, Alex Comfort.....(Mar) 257
Editorial .....(Mar) 235
Correspondence .....(May) 450
Correspondence, Joe N. Ham.....(May) 450
Correspondence, Basil R. Meyerowitz.....(Jun) 549
Why Patients Choose Homeopathy, Robert L. Avina, Lawrence J. Schneiderman.....(Apr) 366

Commitment Process for Psychiatric Patients, The—Changing Status in the Western States (Medical Progress), James H. Shore.....(Mar) 207
Compensable Events, see *Study of Potentially*
Components, Blood, see *Blood Transfusion*
Congenital Heart Disease, see *Differential Diagnosis . . . in Newborn*
Contingency Fee, The (Correspondence), L. Ward Wiseman.....(Feb) 172
Continuing Medical Education, see *Planning*
Continuing Medical Education in Midpassage (Medical Education), Phil R. Manning.....(Mar) 260
[Controlled Substances (Psychotropic Drugs)], see *FDA—The 11th Myth*
Correction: Anastomosis (Correspondence), Max J. Trummer.....(Jan) 74

Correspondence:
Abortion Crisis, The—A Countervailing View, James H. Ford.....(Mar) 255
Contingency Fee, The, L. Ward Wiseman....(Feb) 172
Correction: Anastomosis, Max J. Trummer..(Jan) 74
FDA—The 11th Myth [Amphetamines, Controlled Substances (Psychotropic Drugs)] J. T. Ungerleider.....(Feb) 173
Correspondence, David E. Smith.....(May) 449
Reply, Donald Kennedy.....(Mar) 254
Correspondence, David E. Smith.....(May) 449
Correspondence, James S. Ketchum....(May) 450
Gerontology and Geriatrics, Joe N. Ham....(May) 450
Information Systems [Libraries in Smaller Hospitals] for Small Medical Communities, Richard D. Frank, Mary Widmeyer.....(Feb) 170
Authors' Reply, Norman F. Seidenberg, Bernice Quinn.....(Apr) 354
Correspondence, Keith E. Vincent.....(Apr) 354
Informed Opinion or Assault, David Leigh Rodgers.....(Feb) 171
Local Physicians, PSRO's and HSA's, Albert G. Clark.....(Jun) 548
Mesothelioma in Shipyard Workers, M. Ward Hinds.....(Feb) 169
Monumental Squeak, A [Re Utilization Review and Medical Audit], Arthur D. Silk.....(Jan) 73
More on Health Practitioners, Gary E. Pakes.(Feb) 171
More on Libraries:
Norman F. Seidenverg, Bernice Quinn....(Apr) 354
Keith E. Vincent.....(Apr) 354
More on 'The 11th Myth' About FDA:
David E. Smith.....(May) 449
James S. Ketchum.....(May) 450
New Dimension to Medicine, A, Kong Meng Tan.....(Jun) 548
Of Pediatrics and Geriatrics, Basil R. Meyerowitz.....(Jun) 549
Outpatient Cardiac Catheterization, David A. Ciraulo, Gerald F. Bresnahan, William R. Zimmerman, Robert B. Chesne.....(Jan) 72
Outpatient Self-Administration of Parenteral Antibiotics, Andre N. Minuth.....(May) 452
President Lincoln's Illness, Walter T. Flaherty.....(Apr) 351
Reply, Harold Schwartz.....(Jun) 550
Psychogenic Rheumatism, Michael David Roback.....(Jun) 549

Registered Nurses and Long-Term Care, Pierre Salmon....(Apr) 353
Science and the Art [of Medicine], Edward Palmer....(Apr) 351
Science and the Art [of Medicine], Albert E. Warrens....(Mar) 256
Success Rates in Cardiopulmonary Resuscitation, Michael Eliastam....(Jun) 547
Reply, George H. Hess....(Jun) 547
Survival in Lung Cancer, David J. Rickles, Robert G. Parker, D. Jeffrey Demanes....(Jan) 71
Reply, Ralph D. Reynolds, Bernard R. Greenberg, James H. Shirley....(Jan) 71
Thoracic Outlet Syndrome, Lionel A. Walpin....(May) 451
Traumatic Fibromyositis, Essam A. Awad...(Jan) 68
Reply, Laurence M. Weinberger....(Jan) 68
Traumatic Fibromyositis or Myofascial Trigger Points?, David G. Simons....(Jan) 69
Trends in Obstetrics, E. R. W. Fox....(Apr) 352

[Costs, Medical], see *Ailing Health Care System*
Court Decisions, see *Psychiatric Treatment*
Crisis, see *Abortion*
Crohn Disease—Newer Aspects of Etiology, Diagnosis and Therapy (Medical Staff Conference) ....(May) 419

D

Death Act, see *California's Natural*
Death on Denali: Fatalities Among Climbers in Mount McKinley National Park from 1903 to 1976—Analysis of Injuries, Illnesses and Rescues in 1976, Rodman Wilson, William J. Mills, Jr., Donald R. Rogers....(Jun) 471
Editorial, Herbert N. Hultgren....(Jun) 536
Democracy and Health Care, see *Participatory*
Denali (Mount McKinley) see *Death on*
Determinants in Chronic Hepatitis B, see *Prognostic*
Diagnosing Megaloblastic Anemias (Editorial), Victor Herbert....(Apr) 338
Diagnostic Clues in Metastatic Lesions of Endocarditis in Addicts, Haragopal Thadepalli, Charles K. Francis ....(Jan) 1
Differential Diagnosis of Congenital Heart Disease in the Newborn (UC, San Diego, and University Hospital, San Diego, Interdepartmental Conference), Participants: Stanley E. Kirkpatrick, Adaline Corrin, Charles Higgins, William L. Nyhan....(Feb) 127
Editorial, Alexander S. Nadas....(Feb) 157
Disorders, see *Lithium Treatment for Psychiatric*
Diverticulum, see *Giant Sigmoid*
'Do As I Say' (Editorial)....(Jan) 58
[Drug] Overdose, see *Phenytoin*
Ductus Arteriosus, see *Management of Premature Infant*

E

Eastern and Western Approaches to Medicine, Julia J. Tsuei....(Jun) 551

Editorials: (General and Scientific)

General:

Assault Upon the Professions, The....(Jun) 534
Avicenna Revisited [Iranian Medical School], Lloyd H. Smith, Jr....(Feb) 151
'Do As I Say'....(Jan) 58
Health Systems Agencies [HSA's] and Local Physicians ....(Apr) 337
Correspondence, Albert G. Clark....(Jun) 548
Correspondence, Kong Meng Tan....(Jun) 548
Participatory Democracy and Health Care...(May) 434
Medicine in Ponape....(May) 436
Public Views of NHI....(Mar) 237
Step in the Right Direction....(Jan) 54
Study of Potentially Compensable Events [Medical Insurance Feasibility Study] ....(Apr) 339
Thoughts About Geriatrics....(Mar) 235
Correspondence, Joe N. Ham....(May) 450

Scientific:

Adult Respiratory Distress Syndrome—What To Do Until the Basic Scientist Comes, Philip C. Hopewell....(May) 435
Cholesterol Metabolism and Human Disease, John A. Glomset....(Jan) 55
Diagnosing Megaloblastic Anemias, Victor Herbert....(Apr) 338
Lithium Treatment, Mogens Schou....(Jun) 535
Management of Asthma, Oscar L. Frick....(May) 437
Medicine in Ponape....(May) 436
Modern View of Ataxia, Pieter Kark....(Jun) 537
Newborn Infants With Congenital Heart Disease, Alexander S. Nadas....(Feb) 157
Paraquat Poisoning: An Update, Ronald D. Fairshter....(Jan) 56
Patent Ductus Arteriosus, Michael A. Heymann....(Mar) 238
Prevention of Meningococcal Disease: Practice and Prospects, Theodore C. Eickhoff....(Mar) 236
Prognostic Determinants in Chronic Hepatitis B Infection—A Reevaluation, James L. Boyer..(Apr) 340
Progress With Hepatitis B Virus (Editorial Review), William S. Robinson....(Feb) 153
Risks of [Mountain] Climbing, Herbert N. Hultgren....(Jun) 536
Trends in the Science and the Art....(Feb) 152
Correspondence, Albert E. Warrens....(Mar) 256
Correspondence, Edward Palmer....(Apr) 351

Education, see *Continuing Medical*
Education, see *Planning Continuing Medical*
Education Center, Health, see *Central San Joaquin*
Elements, see *Trace*
Embolectomy, see *Pulmonary*
Embolus, Pulmonary, see *Rapid Resolution*
Emphysema, see *Retroperitoneal*
Encephalitis, see *St. Louis*
Endocarditis in Addicts, see *Diagnostic Clues*
Epidemiology, see *Meningococcal Disease*

Epitomes:

Pathology ....(Jan) 46
Anesthesiology ....(Feb) 142
Pediatrics ....(Mar) 228
Radiology ....(Apr) 331
Ophthalmology ....(May) 428
Plastic Surgery ....(Jun) 527

Esophageal Ulceration Caused by Wax-Matrix Potassium Chloride [Slow-K®], Jeffrey Riker, Margo Swanson, Byron Schweigert....(Jun) 542
[Ethics, Medical], see *Ailing Health Care System*
Examinations, Physical, see *Legal Implications*

F

Factors Influencing the Location of Rural General Practitioners—A Study in Washington State (Health Care Delivery), Sam M. Cordes...(Jan) 75
Fatalities Among Climbers, see *Death on Denali*
Feasibility of Outpatient Self-Administration of Parenteral Antibiotics, Andris Antoniskis, Bruce C. Anderson, Earl J. Van Volkinburg, Joanne M. Jackson, David N. Gilbert.....(Mar) 203
Correspondence, Andre N. Minuth.....(May) 452
Feasibility Study, see *Medical Insurance*
FDA—The 11th Myth [Amphetamines, Controlled Substances (Psychotropic Drugs)] (Correspondence), J. T. Ungerleider.....(Feb) 173
Correspondence, David E. Smith.....(May) 449
Reply, Donald Kennedy.....(Mar) 254
Correspondence, David E. Smith.....(May) 449
Correspondence, James S. Ketchum....(May) 450
Femoral Tibial Bypass Grafts—The Alternatives to Amputation, Gordon Sproul.....(Apr) 291
Fibromuscular Hyperplasia of External Iliac Arteries, Michael K. Daskalakis.....(Apr) 345
Fibromyositis, see *Traumatic*
Fistula, see *Tracheoesophageal*
[Food and Drug Administration], see FDA

G

General Practitioners, see *Factors Influencing*
Geriatrics, see *Gerontology*
Geriatrics, see *Of Pediatrics and*
Geriatrics, see *Thoughts About*
Geriatrics—The Missing Discipline (Commentary), Alex Comfort.....(Mar) 257
Editorial .....(Mar) 235
Correspondence, Joe N. Ham.....(May) 450
Correspondence, Basil R. Meyerowitz.....(Jun) 549
Gerontology and Geriatrics (Correspondence), Joe N. Ham.....(May) 450
Giant Sigmoid Diverticulum, Raymond M. Wetrich, Dip S. Sidhu.....(Jun) 539
[Government and Medicine], see *Health Systems Agencies*
Grafts, see *Femoral Tibial Bypass*
Graves Hyperthyroidism Following Myxedema in a Patient with Recurrent Colon Carcinoma, Gerald A. Levine, Donald E. Williams, Jerome M. Hershman, Gildon N. Beall.....(Mar) 240

H

[Head and Neck Injuries], see *Thoracic Outlet*
Head Injury and Early Signs of Tentorial Herniation—A Management Dilemma, Julian T. Hoff, Robert Spetzler, David Winestock.....(Feb) 112
Health Care, see *Participatory Democracy*

Health Care Delivery:

Factors Influencing the Location of Rural General Practitioners—A Study in Washington State, Sam M. Cordes.....(Jan) 75
Medical School Graduates Who Leave California—A Study at the University of California, San Francisco, Harrison G. Gough, Wallace B. Hall.(Jan) 81

Health Care System, see *Ailing*

Health Care Team:

Health Screening and the Role of Nurse Assistants—Medicolegal Considerations in California, Henry B. Bruyn, Susan Crocker.....(Feb) 178

Health Education Center, see *Central San Joaquin Valley*
[Health Insurance, National], see *Public Views*
Health Practitioners, see *More on*
Health Screening and the Role of Nurse Assistants—Medicolegal Considerations in California (Health Care Team), Henry B. Bruyn, Susan Crocker.....(Feb) 178
Health Systems Agencies [HSA's] and Local Physicians (Editorial).....(Apr) 337
Correspondence, Albert G. Clark.....(Jun) 548
Correspondence, Kong Meng Tan.....(Jun) 548
Heart Disease, Congenital, see *Differential Diagnosis . . . in Newborn*
[Hematologic Diseases], see *Hereditary Spherocytosis*
Hematoma, see *Splenic Subcapsular*
Hemochromatosis (Medical Staff Conference).(Feb) 133
Hemodialysis, see *Acute Renal Failure*
Hemophilus influenzae, see *Ampicillin-Resistant*
Hepatitis, see *Anorectal Lesions and Syphilitic*
Hepatitis, see *Viral*
Hepatitis B, see *Chronic*
Hepatitis B Infection, see *Prognostic Determinants*
Hepatitis B Virus, see *Progress With*
Hereditary Spherocytosis Revisited—Eighth Annual Paul M. Aggeler Memorial Lecture, Lecturer: William N. Valentine (Medical Staff Conference) .....(Jan) 35
Herniation, Tentorial, see *Head Injury*
Homeopathy, see *Why Patients Choose*
Hospitals, Rural, see *Cardiopulmonary Resuscitation*
[HSA's], see *Health Systems Agencies*
HSA's, see *Local Physicians*
Human Rabies, Larry J. Barraff, Barry Hafkin, Paul F. Wehrle, Richard W. Emmons, Robert Gunn, Gary D. Overturf.....(Feb) 159
Human Disease, see *Cholesterol Metabolism*
Hyperplasia, see *Fibromuscular*
Hyperthyroidism, see *Graves*
Hypervitaminosis A, see *Cirrhosis Due to*
Hypophosphatemia, see *Acute Renal Failure*
Hysteria, see *Management of Briquet Syndrome*

I

Iliac Arteries, see *Fibromuscular Hyperplasia*
[IMCI (Imperial Medical Center of Iran)], see *Avicenna Revisited*
[Imperial Medical Center of Iran], see *Avicenna Revisited*
Important Advances in Clinical Medicine, see *Epitomes*
Immune Complex Pathogenesis, see *Vasculitis . . . Propylthiouracil*
Infant, Premature, with Patent Ductus Arteriosus, see *Management*
Infants With Congenital Heart Disease, see *Newborn*
[Inflammatory Bowel Disease], see *Crohn Disease*
Influenzae, Hemophilus, see *Ampicillin-Resistant*

Information:
(See also Medical Information)

Munchausen Syndrome Presenting as Urolithiasis, William A. Jones, Thomas P. Cooper, Mark D. Kiviat ..... (Feb) 185

Information Systems [Libraries in Smaller Hospitals] for Small Medical Communities (Correspondence), Richard D. Frank, May Widmeyer ..... (Feb) 170
Authors' Reply, Norman Seidenverg, Bernice Quinn ..... (Apr) 254
Correspondence, Keith E. Vincent ..... (Apr) 254
Informed Opinion or Assault? (Correspondence), David Leigh Rodgers ..... (Feb) 171
Injury, see *Head*
[Insurance, National Health], see *Public Views*
Insurance Feasibility Study, see *Medical*
Intercity Outbreak of Meningococcal Meningitis in Adults, An, Phyllis A. Oill, Anthony W. Chow, Ronald R. Roberto, Lucien B. Guze ..... (Mar) 189
Editorial, Theodore C. Eickhoff ..... (Mar) 236
Intestinal Parasites, see *Venereal Transmission*
[Involuntary Hospitalization], see *Psychiatric Treatment*
Ipecac Poisoning, James S. Miser, William O. Robertson ..... (May) 440
[Iran, Imperial Medical Center of], see *Avicenna Revisited*

J

John Wesley County Hospital, Los Angeles, see *Specialty Conferences*

L

Laboratory Diagnosis of Megaloblastic Anemias, The (Medical Progress), Ralph Carmel ... (Apr) 294
Editorial, Victor Herbert ..... (Apr) 338
Legal Implications of Physical Examinations, Jean Spencer Felton ..... (Mar) 266
Legionnaires Disease Causing Adult Respiratory Distress Syndrome—Survival and Report of Open Lung Biopsy, Richard A. Nusser, Mitchell P. Tarkoff ..... (May) 443
Libraries, see *More On*
[Libraries, Medical], see *Information Systems*
Lincoln, see *Abraham*
Lincoln's Health, see *Abraham Lincoln and Cardiac Decompensation*
Lincoln's Illness, see *President*
Lithium Treatment for Psychiatric Disorders (Medical Progress), Barry M. Maletzky, James H. Shore ..... (Jun) 488
Editorial, Mogens Schou ..... (Jun) 535
Local Physicians, see *Health Systems Agencies*
Local Physicians, PSRO's and HSA's (Correspondence), Albert G. Clark ..... Jun) 548
Location of Rural General Practitioners, see *Factors Influencing*
Long-Term Care, see *Registered Nurses*
Lung Biopsy, Open, see *Legionnaires Disease*
Lung Cancer, see *Survival*

M

Malformations, see *Tracheoesophageal Fistula*
Malignant Pheochromocytoma, see *Treatment*
Management of Asthma (Editorial), Oscar L. Frick ..... (May) 437
Management of Briquet Syndrome (Hysteria), James R. Morrison ..... (Jun) 482
Management of the Premature Infant With Patent Ductus Arteriosus (University of California, San Diego, and University Hospital, San Diego, Interdepartmental Conference), Participants: T. Allen Merritt, Louis Gluck, Charles Higgins, William L. Nyhan ..... (Mar) 212
Editorial, Michael A. Heymann ..... (Mar) 238
[Marijuana], see *FDA—The 11th Myth*
McKinley, Mount, see *Death on Denali*
[Medical Audit], see *Monumental Squeak*
Medical Education, see *Planning Continuing*

Medical Education:

Unprofessional Physicians—Some Correlative Data, G. Gordon Hadley, Jere E. Chrispens ..... (Jan) 85
Continuing Medical Education in Midpassage, Phil R. Manning ..... (Mar) 260
Central San Joaquin Valley Area Health Education Center, Edwin F. Rosinski ..... (Apr) 355
Medical Resident in Ponape [South Pacific], Alan C. Nelsen ..... (May) 453
Editorial ..... (May) 436
Planning Continuing Medical Education Activities, Floyd C. Pennington ..... (Jun) 558

Medical Information:

Venereal Transmission of Intestinal Parasites, Alfred L. Hurwitz, Robert L. Owen ..... (Jan) 89
Munchausen Syndrome Presenting as Urolithiasis, William A. Jones, Thomas P. Cooper, Mark D. Kiviat ..... (Feb) 185
Tracheoesophageal Fistula and Associated Malformations, C. Richard Dewar, Stephen R. Shapiro, David F. Merten ..... (Apr) 370

Medical Insurance Feasibility Study—A Technical Summary, Don Harper Mills ..... (Apr) 360
Editorial ..... (Apr) 339

Medical Jurisprudence:

Psychiatric Treatment—General Implications and Lessons from Recent Court Decisions in California, Edward Rudin, Rick Zimmerman .. (May) 459

[Medical Libraries], see *Information Systems*

Medical Progress:

Cholesterol Metabolism in Man, Scott M. Grundy ..... (Jan) 13
Editorial, John A. Glomset ..... (Jan) 55
Viral Hepatitis, Gary L. Gitnick ..... (Feb) 117
Editorial, William S. Robinson ..... (Feb) 153
Commitment Process for Psychiatric Patients—Changing Status in the Western States, James H. Shore ..... (Mar) 207
Laboratory Diagnosis of Megaloblastic Anemias, Ralph Carmel ..... (Apr) 294
Editorial, Victor Herbert ..... (Apr) 338
Adult Respiratory Distress Syndrome, Thomas L. Petty, John H. Newman ..... (May) 399
Editorial, Philip C. Hopewell ..... (May) 435
Lithium Treatment for Psychiatric Disorders, Barry M. Maletzky, James H. Shore ..... (Jun) 488
Editorial, Mogens Schou ..... (Jun) 535

Medical Resident in Ponape [South Pacific] (Medical Education), Alan C. Nelson.....(May) 453
Editorial .....(May) 436
Medical School Graduates Who Leave California—A Study at the University of California, San Francisco (Health Care Delivery), Harrison G. Gough, Wallace B. Hall.....(Jan) 81

Medical Staff Conferences:

Hereditary Spherocytosis Revisited—Eighth Annual Paul M. Aggeler Memorial Lecture, Lecturer: William N. Valentine.....(Jan) 35
Hemochromatosis, Chief Discussant: Lloyd H. Smith, Jr.....(Feb) 133
Trace Elements, Chief Discussant: Faith Fitzgerald.....(Mar) 223
California's Natural Death Act, Moderator: H. Harrison Sadler; Participants: Julius R. Krevans, Benson R. Roe, Barry Keene, Albert Jonsen, John Solters, Kathleen R. Lavery, Elaine Fripp, Hillary Don, Jerome Lackner.....(Apr) 318
Appendix: Survey Results After One Year's Experience, Murray Klutch.....(Apr) 329
Crohn Disease—Newer Aspects of Etiology, Diagnosis and Therapy, Chief Discussants: John P. Cello, Ruedi F. Thoeni.....(May) 419
Ailing Health Care System, The, Discussants: Philip R. Lee, William Bradley, Steven A. Schroeder, Craig Lubin, Albert R. Jonsen, William B. Kerr, Lewis H. Butler.....(Jun) 512

Medicolegal, see *Health Screening*
Medicine, see *Eastern and Western Approaches*
Medicine, see *New Dimension*
Medicine in Ponape (Editorial).....(May) 436

Medicine in American History:

Abraham Lincoln and Cardiac Decompensation—A Preliminary Report, Harold Schwartz...(Feb) 174
Correspondence, Walter T. Flaherty.....(Apr) 351
Reply, Harold Schwartz.....(Jun) 550

Megaloblastic Anemias, see *Diagnosing*
Megaloblastic Anemias, see *Laboratory Diagnosis*
Meningitis, see *Intercity Outbreak*
Meningococcal Disease in California: Epidemiology and Management, Charles Juels, Florence R. Morrison, Gary D. Overturf, Ronald R. Roberto, James Chin.....(Mar) 195
Editorial, Theodore C. Eickhoff.....(Mar) 236
Meningococcal Meningitis, see *Intercity Outbreak*
[Meningoencephalitis, Acute Viral], see *Human Rabies*
Mesothelioma in Shipyard Workers (Correspondence), M. Ward Hinds.....(Feb) 169
Metabolism in Man, see *Cholesterol*
Metastatic Lesions of Endocarditis, see *Diagnostic Clues*
Midpassage, see *Continuing Medical Education in*
Modern View of Ataxia (Editorial), Pieter Kark.....(Jun) 537
Monumental Squeak, A [Re Utilization Review and Medical Audit] (Correspondence), Arthur D. Silk.....(Jan) 73
More on Health Practitioners (Correspondence), Gary E. Pakes.....(Feb) 171
More on Libraries (Correspondence):
Norman F. Seidenverg, Bernice Quinn....(Apr) 254
Keith E. Vincent.....(Apr) 254
More on 'The 11th Myth' About FDA (Correspondence):
David E. Smith.....(May) 449
James S. Ketchum.....(May) 450
Mount McKinley National Park, see *Death on Denali*
[Mountain] Climbers, Injuries, Illnesses and Rescues, see *Death on Denali*
[Mountain] Climbing, see *Risks of*
Munchausen Syndrome Presenting as Urolithiasis (Information), William A. Jones, Thomas P. Cooper, Mark D. Kiviat.....(Feb) 185
Myofascial Trigger Points, see *Traumatic Fibromyositis*
Myxedema, see *Graves Hyperthyroidism*

N

Natural Death Act, see *California's*
[National Health Insurance], see *Public Views*
[Neck Injuries], see *Thoracic Outlet*
New Dimension to Medicine, A (Correspondence), Kong Meng Tan.....(Jun) 548
Newborn, Congenital Heart Disease in, see *Differential*
Newborn Infants With Congenital Heart Disease (Editorial), Alexander S. Nadas.....(Feb) 157
NHI, see *Public Views*
Nurse Assistants, see *Health Screening*
Nurses and Long-Term Care, see *Registered*

O

Obstetrics, see *Trends in*
[Occupationally Incurred Disease], see *Legal Implications of Physical Examinations*
Of Pediatrics and Geriatrics (Correspondence), Basil R. Meyerowitz.....(Jun) 549
Ophthalmology, see *Epitomes*
Outbreak of Meningococcal Meningitis, see *Intercity*
Outpatient Cardiac Catheterization, David A. Ciraulo, Gerald F. Bresnahan, William R. Zimmerman, Robert B. Chesne (Correspondence) .....(Jan) 72
Outpatient Self-administration of Parenteral Antibiotics, see *Feasibility*
Outpatient Self-Administration of Parenteral Antibiotics (Correspondence), Andre N. Minuth.....(May) 452
Overdose, see *Phenytoin*

P

Parenteral Antibiotics, see *Feasibility of Outpatient*
Parenteral Antibiotics, see *Outpatient Self-Administration*
Paraquat Ingestion and Pulmonary Injury (Stanford University Pulmonary Rounds) (Specialty Conference), Participants: Judith Pickersgill, Eugene D. Robin, James Theodore, Thomas A. Raffin, Paul David Laman, Lawrence M. Simon...(Jan) 26
Editorial, Ronald D. Fairshter.....(Jan) 56
Parasites, see *Venereal Transmission*
Participatory Democracy and Health Care (Editorial) .....(May) 434
Patent Ductus Arteriosus, see *Management of Premature Infant*
Pathogenesis and Response to Therapy, see *Vasculitis . . . Propylthiouracil*

Pathology, see *Epitomes*
Paul M. Aggeler Memorial Lecture, see *Hereditary Spherocytosis*
Pediatrics, see *Epitomes*
Pediatrics, see *Of . . . and Geriatrics*
[Persia], see *Avicenna Revisited*
Phenytoin Overdose Kinetics, Mark A. Gill, Jack W. Kern, Jeanne Kaneko, James McKeon, Charles Davis . . . . . (Mar) 246
Pheochromocytoma, see *Treatment of Malignant*
Physical Examinations, see *Legal Implications*
[Physician's Assistants], see *Health Screening*
Physicians, see *Health Systems Agencies and*
Physicians, see *Unprofessional*
Physicians, PSRO's and HSA's, see *Local*
Planning Continuing Medical Education Activities (Medical Education), Floyd C. Pennington . (Jun) 558
Plastic Surgery, see *Epitomes*
Poisoning, see *Ipecac*
Poisoning, see *Paraquat*
Polypectomy, Colonoscopic, see *Retroperitoneal Emphysema*
Ponape, see *Medical Resident*
Potassium Chloride, see *Esophageal Ulceration*
Premature Infant with Patent Ductus Arteriosus, see *Management*
President Lincoln's Illness, see *Abraham Lincoln*
Prevention of Meningococcal Disease: Practice and Prospects (Editorial), Thomas C. Eickhoff . (Mar) 236
Professions, see *Assault Upon*
Prognostic Determinants in Chronic Hepatitis B Infection—A Reevaluation (Editorial), James L. Boyer . . . . . (Apr) 340
Progress With Hepatitis B Virus (Editorial Review), William S. Robinson . . . . . (Feb) 153
Proposed Constitutional Amendments (CMA) . (Jan) 98
Propylthiouracil, see *Vasculitis Associated With*
PSRO's, see *Local Physicians*
Psychiatric Disorders, see *Lithium Treatment*
Psychiatric Patients, see *Commitment Process*
Psychiatric Treatment—General Implications and Lessons from Recent Court Decisions in California, Edward Rudin, Rick Zimmerman . . (May) 459
Psychogenic Rheumatism, see *Clinical Diagnosis*
Psychogenic Rheumatism (Correspondence), Michael David Roback . . . . . (Jun) 549
Psychosurgery, see *Psychiatric Treatment . . . Court Decisions*
[Psychotropic Drugs], see *FDA—The 11th Myth*
Public Views of NHI (Editorial) . . . . . (Mar) 237
[Puget Sound], see *Mesothelioma in Shipyard Workers*
Pulmonary Embolectomy, Argun Saylam, Joao Q. Melo, Aftab Ahmad, Richard D. Chapman, James A. Wood, Albert Starr . . . . . (May) 377
Pulmonary Embolus, see *Rapid Resolution*
Pulmonary Injury, see *Paraquat Ingestion*

R

Rabies, see *Human*
Radiology, see *Epitomes*
Rapid Resolution of a Pulmonary Embolus in Man, Walter S. James III, Stuart J. Menn, Kenneth M. Moser . . . . . (Jan) 60
Registered Nurses and Long-Term Care (Correspondence), Pierre Salmon . . . . . (Apr) 353
Renal Failure, see *Acute*
Resident [Physician] in Ponape, see *Medical*
Respiration During Sleep in Children, Mary A. Carskadon, Kim Harvey, William C. Dement, Christian Guilleminault, F. Blair Simmons, Thomas F. Anders . . . . . (Jun) 477
Respiratory Distress Syndrome, see *Adult*
Respiratory Distress Syndrome, see *Legionnaires Disease*
Resuscitation, see *Cardiopulmonary*
Retroperitoneal Emphysema After Colonoscopic Polypectomy, Sidney Yassinger, Robert C. Midgley, David S. Cantor, Tommy Poirier, Thomas J. Imperato . . . . . (Apr) 347
Rheumatism, see *Clinical Diagnosis*
Risks of [Mountain] Climbing (Editorial), Herbert N. Hultgren . . . . . (Jun) 536
Rural Community Hospitals, see *Cardiopulmonary Resuscitation*
Rural General Practitioners, see *Factors Influencing*

S

Sacramento Medical Center, see *Specialty Conferences*
San Francisco General Hospital, see *Medical Staff Conferences*
San Joaquin Valley Area Health Education Center, see *Central*
Science and the Art, Trends in (Editorial) . . . (Feb) 152
Correspondence, Albert E. Warrens . . . . . (Mar) 256
Correspondence, Edward Palmer . . . . . (Apr) 351
Screening, see *Health*
Self-Administration of Parenteral Antibiotics, see *Feasibility of Outpatient*
Self-Administration of Parenteral Antibiotics, see *Outpatient*
Seminars in Virology: A Biological Perspective of Slow Virus Infection and Chronic Disease, Joseph W. St. Geme, Jr. . . . . (May) 382
Shipyard Workers, see *Mesothelioma*
Sigmoid Diverticulum, see *Giant*
[Sleep Apnea Syndrome in Children], see *Respiration During Sleep*
[Slow-K®,] see *Esophageal Ulceration Caused by*
Slow Virus, see *Seminars in Virology*
[South Pacific], see *Medical Resident in Ponape*

Special Articles:

Legal Implications of Physical Examinations, Jean Spencer Felton . . . . . (Mar) 266
Medical Insurance Feasibility Study—A Technical Summary, Don Harper Mills . . . . . (Apr) 360
Editorial . . . . . (Apr) 339
Eastern and Western Approaches to Medicine, Julia J. Tsuei . . . . . (Jun) 551

Specialty Conferences:

Paraquat Ingestion and Pulmonary Injury (Stanford University Pulmonary Rounds), Participants: Judith Pickersgill, Eugene D. Robin, James Theodore, Thomas A. Raffin, Paul David Laman, Lawrence M. Simon . . . . . (Jan) 26
Editorial, Ronald D. Fairshter . . . . . (Jan) 56
Differential Diagnosis of Congenital Heart Disease in the Newborn (UC, San Diego, and University Hospital, San Diego, Interdepartmental Conference, Pediatrics, and Radiology), Participants: Stanley E. Kirkpatrick, Adaline Corrin, Charles

Higgins, William L. Nyhan.....(Feb) 127
Editorial, Alexander S. Nadas.....(Feb) 157
Management of the Premature Infant with Patent Ductus Arteriosus (UC, San Diego, and University Hospital, San Diego, Interdepartmental Conference, Pediatrics and Radiology), Participants: T. Allen Merritt, Louis Gluck, C. Charles Higgins, William Friedman, William L. Nyhan....(Mar) 212
Editorial, Michael A. Heymann.....(Mar) 238
Chronic Hepatitis B (USC School of Medicine and John Wesley County Hospital), Participants: John C. Hoefs, Robert L. Peters, Allan G. Redeker, Myron J. Tong, James W. Mosley, Telfer B. Reynolds.....(Apr) 305
Editorial, James L. Boyer.....(Apr) 340
An Approach to the Treatment of Asthma (UC, San Diego, and UC Medical Center, San Diego, Pediatric Conference), Participants: Michael Mellon, Gary I. Incaudo, Stephen Kahler, Robert N. Hamburger, William L. Nyhan.....(May) 408
Editorial, Oscar L. Frick.....(May) 437
Cerebellar Ataxia: Anatomical, Physiological and Clinical Implications (UC, Davis, and Sacramento Medical Center), Participants: Pierre M. Dreyfus, Meherji Oshtory, Ernest D. Gardner, James S. Lieberman, Nashiyath Vijayan.....(Jun) 499
Editorial, Pieter Kark.....(Jun) 537

Spherocytosis, see *Hereditary*
Splenic Subcapsular Hematoma—Ultrasonic Diagnosis, Robert L. Wilson, William F. Rogers, Michael S. Shaub, William Birnbaum.....(Jan) 6
Stanford University, see *Specialty Conferences*
Step in the Right Direction (Editorial).....(Jan) 54
St. Louis Encephalitis in Children, Allen M. Kaplan, William L. Longhurst, Donald L. Randall.(Apr) 279
Study of Potentially Compensable Events (Editorial) .....(Apr) 339
Success Rates in Cardiopulmonary Resuscitation (Correspondence), Michael Eliastam.....(Jun) 547
Reply, George H. Hess.....(Jun) 547
Survey Results After One Year's Experience With The Natural Death Act (Appendix, Medical Staff Conference), Murray Klutch.....(Apr) 329
Survival in Lung Cancer (Correspondence), David J. Rickles, Robert G. Parker, D. Jeffery Demanes.....(Jan) 71
Reply, Ralph D. Reynolds, Bernard R. Greenberg, James H. Shirley.....(Jan) 71
Syphilitic Hepatitis, see *Anorectal Lesions*
System, see *Ailing Health Care*

T

Tachycardia . . . with an Apical Aneurysm, see *Ventricular*
Tentorial Herniation, see *Head Injury*
Thoracic Outlet Syndrome, Ward W. Woods..(Jan) 9
Correspondence, Lionel A. Walpin.....(May) 451
Thoughts About Geriatrics (Editorial).....(Mar) 235
Correspondence, Joe N. Ham.....(May) 450
Thyroiditis, see *Acute Suppurative*
Tibial Bypass Grafts, see *Femoral*
Trace Eelements (Medical Staff Conference).(Mar) 223
Tracheoesophageal Fistula and Associated Malformations (Medical Information), C. Richard Dewar, Stephen R. Shapiro, David F. Merten.....(Apr) 370
Transmission of Intestinal Parasites, see *Venereal*
Transfusion, see *Blood*
Traumatic Fibromyositis (Correspondence), Essam A. Awad.....(Jan) 68
Reply, Laurence A. Weinberger.....(Jan) 68
Traumatic Fibromyositis or Myofascial Trigger Points? (Correspondence), David G. Simons.....(Jan) 69
Treatment for Psychiatric Disorders, see *Lithium*
Treatment of Malignant Pheochromocytoma, Harry Drasin.....(Feb) 106
Trends in Obstetrics (Correspondence), E. R. W. Fox.....(Apr) 352
Trends in the Science and the Art (Editorial).(Feb) 152
Correspondence, Albert E. Warrens.....(Mar) 256
Correspondence, Edward Palmer.....(Apr) 351

U

UC, Davis, see *Specialty Conferences*
UC, San Diego, see *Specialty Conference*
UC, San Francisco, see *Medical School Graduates*
UC, San Francisco, see *Medical Staff Conferences*
Ulceration, see *Esophageal*
Ultrasonic Diagnosis, see *Splenic Subcapsular Hematoma*
University Hospital, San Diego, see *Specialty Conferences*
Unprofessional Physicians—Some Correlative Data (Medical Education), G. Gordon Hadley, Jere E. Chrispens.....(Jan) 85
Urolithiasis, see *Munchausen Syndrome*
USC School of Medicine, see *Specialty Conferences*
[Utilization Review], see *Monumental Squeak*

V

Vasculitis Associated With Propylthiouracil—Evidence for Immune Complex Pathogenesis and Response to Therapy, William R. Griswold, Stanley A. Mendoza, William Johnston, Steven Nichols.....(Jun) 543
[VATER Association], see *Tracheoesophageal Fistula*
[Venereal Disease], see *Anorectal Lesions*
Venereal Transmission of Intestinal Parasites (Medical Information), Alfred L. Hurwitz, Robert L. Owen.....(Jan) 89
Ventricular Tachycardia in a Young Adult with an Apical Aneurysm, W. Allan Edmiston, Taro Yokoyama, Jerome Kay, Michael Bilitch, Francis Y. K. Lau.....(Mar) 248
[Viral] Hepatitis, see *Chronic*
Viral Hepatitis (Medical Progress), Gary L. Gitnick.....(Feb) 117
Editorial, William S. Robinson.....(Feb) 153
Virology, see *Seminars in*
Virus, see *Progress With Hepatitis B*
Virus Infection, see *Seminars in Virology*
Vitamin A, see *Cirrhosis Due to*

W

Washington State, see *Factors Influencing Location of Rural General Practitioners*
Wax-Matrix Potassium Chloride [Slow-K®], see *Esophageal Ulceration*
Western Approaches to Medicine, see *Eastern*
Why Patients Choose Homeopathy (Commentary), Robert L. Avina, Lawrence J. Schneiderman.....(Apr) 366

Y

[Yin and Yang], see *Eastern . . . Medicine*
Young Adult, see *Ventricular Tachycardia*

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GENERAL PRACTITIONER for busy group in East Los Angeles. Full time. Spanish speaking helpful. No night or weekend calls; no OB or hospital work. Excellent salary and paid malpractice. MD or DO. Phone (213) 269-0421.

SAN MATEO-SAN MATEO COUNTY: Board Certified or Eligible Family Practitioner to provide care in a multispecialty clinic associated with an acute general hospital. Remuneration based on experience and education. For information contact Bertha Hall, RN, Mgr., Outpatient Clinic, or Selma Kastan, MD, H. D. Chope Community Hospital, 222 W. 39th Ave., San Mateo, CA 94403; (415) 573-2222.

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THE SAN BERNARDINO COUNTY PUBLIC HEALTH DEPARTMENT has immediate openings for qualified physicians with experience and current interest in Communicable Disease, Family Practice or Occupational Medicine; Salary $42,000 range; comprehensive benefits package estimated at 20 percent; licensure in California is mandatory. Interested candidates should direct their inquiries and curriculum vitae to James Carey, MD, Chief Medical Care Division, San Bernardino County Department of Public Health, 351 North Mountain View Ave., San Bernardino, CA 92415; telephone (714) 383-2241.

FEDERALLY QUALIFIED GROUP PRACTICE HMO in San Francisco Bay Area with 10 physicians and 4 nurse practitioners seeks a Medical Director. The candidate should be a Board certified or eligible primary care physician with a minimum of two years administrative experience. The Medical Director, who is the chief medical officer of the HMO, will divide his/her time approximately 50/50 between medical administration duties and practice. Send curriculum vitae to Barbara Winter, Rockridge Health Care Plan, 420 - 40th St., Oakland, CA 94609. EOE

CALIFORNIA—FAMILY PHYSICIAN. University of California, San Francisco-affiliated Family Practice Residency Program in Fresno, California is seeking family physician to join established Family Practice Residency Program. Located at Valley Medical Center of Fresno, the department is developing a residency training program to serve the Central San Joaquin Valley area of California. Candidates should be Board certified/eligible in Family Medicine. Previous clinical teaching experience desirable. Delightful city near national parks. Equal Opportunity Employer. Professional liability paid. Send curriculum vitae with first letter of inquiry to H. John Blossom, MD, Chief of Family Practice, Valley Medical Center of Fresno, 445 South Cedar Ave., Fresno, CA 93702.

CALIFORNIA—INTERNIST. University of California, San Francisco-affiliated hospital in Fresno with nine residency programs is seeking to coordinate and develop internal medicine portion of its Family Practice Residency. The medical school is developing a major clinical branch in Fresno, a delightful city near national parks. Board certification or active candidacy in Internal Medicine and previous experience in education relating to primary care required. Academic appointments available if person qualifies. Equal Opportunity Employer. Professional liability paid. Send curriculum vitae with first inquiry to H. John Blossom, MD, Chief of Family Practice, Valley Medical Center of Fresno, 445 South Cedar Ave., Fresno, CA 93702.

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National Spinal Cord Injury Fellowship

The California Regional Spinal Cord Injury Care System offers a HEW funded Spinal Cord Injury Fellowship at Santa Clara Valley Medical Center to physicians, Board eligible or Board certified, in a medical or surgical related specialty, i.e., Orthopedics, Urology, Neurology, Internal Medicine, etc. The Fellowship is one year in length beginning January, 1979. For further information, write or call (408) 279-5639. **Sheldon Berrol, MD, Chairman PM&R, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, California 95128.**

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SAN DIEGO Family Practitioner seeks Board Certified Internist to share use and expenses of large suite in modern medical office building. Four minutes from three major hospitals. Free patient parking. Pay pro-rata share of rent at $.55 per square foot per month. Reply to Bruce Redmond, MD, 3330 Third Ave., Suite 402, San Diego, CA 92103.

CALIFORNIA BOARD CERTIFIED, RADIOLOGIST for Chief, Radiology Service, needed at VA Hospital, Livermore, CA. Ideal living, good climate. Malpractice insurance not needed. Position is available at present time. Salary dependent on experience and qualifications. Contact: Chief, Personnel Service, Veterans Administration Hospital, Livermore, CA 94550. Tel: (415) 447-2560, ext. 304.

200 - DOCTOR, MULTICLINIC, hospital - based medical group HMO, medical school affiliated, seeks physician experienced in fields of Workers' Compensation and Occupational Medicine to direct an existing growing program presently furnishing medical and health care for 200,000 members (80,000 employed) and 1,300 medical personnel. Development of preventive and health services program for small and large business is future objective. Board certification desirable but experienced physician or one who has completed approved residency will be considered. Incumbent physician retiring July 1978, position available now. Starting salary is negotiable. Excellent benefits package and partnership. Telephone (714) 563-2775 or send résumé in confidence to Herbert Sorensen, MD, Associate Medical Director, Southern California Permanente Medical Group, 4647 Zion Avenue, San Diego, CA 92120.

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ALLERGIST—32 years old, board certified Allergy, Immunology and Pediatrics. California licensed, presently practicing Allergy in Midwest with group. Wishes to relocate. Available July 1978. Associate or group. Box 5977, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 26)

(Continued from Page 25)

SITUATIONS WANTED

PHYSICIAN'S ASSISTANT—recent Duke graduate—desires position in Rocky Mountain states or N.W. Primary care preferred. Call (919) 684-6134 (day). Doug Stackhouse, 4216 Garrett Rd. (M-28), Durham, NC 27707.

RADIOLOGIST with considerable experience in general diagnosis and recent training in CT. Seeking position with a radiology group. Wishes to remain in Northern California. Reply Box 5984, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN, California Licensed, interested in employment at occupational and/or medical outpatient clinic. 4 postgraduate years. Prefer San Francisco or close Bay Area location. 2201 Laguna St., San Francisco, CA 94115; (415) 922-7587 or 929-0708.

CARDIOLOGIST, 31, ABIM, University trained seeks group or hospital-based practice in Southern California. Expertise in cath/coronary angiogram. Write Box 5990, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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SAN MARCOS MEDICAL CENTER — Medical office space for lease in growing No. San Diego County. Need for General or Family Physicians, Internists and some Specialists. Occupancy, January, 1979. Contact Ms. Usher, 1121 La Bonita Dr., San Marcos, CA 92069; (714) 744-3501.

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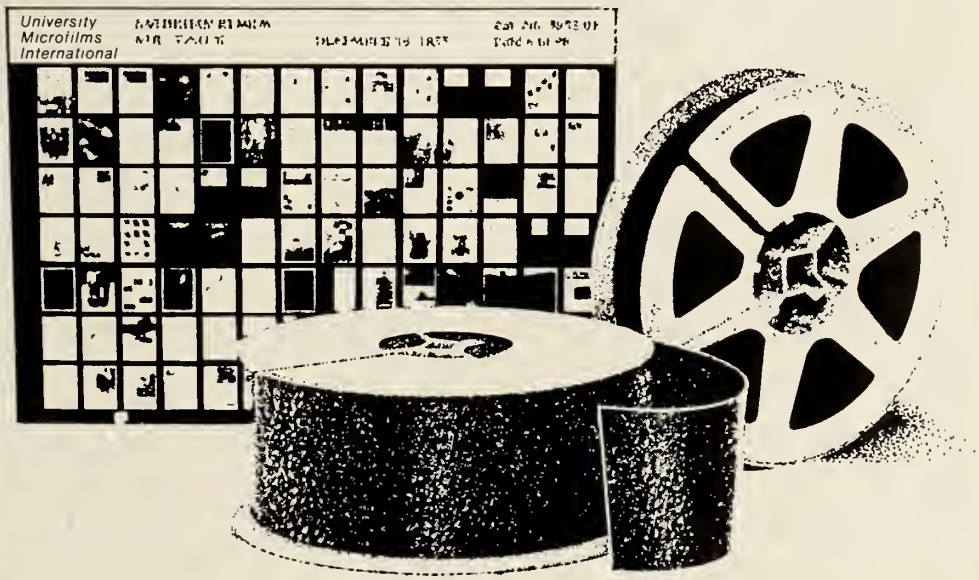

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ADOPTING THE PROBLEM-ORIENTED MEDICAL RECORD IN NURSING HOMES—A Do-It-Yourself Manual—Howard F. Corbus, MD, Assistant Dean for Community Hospital Affairs, University of California, San Francisco, Fresno; Director of Nuclear Medicine, St. Agnes Hospital, Fresno, California; and Laura L. Swanson, RN, Director of Nursing, San Joaquin Gardens, Fresno. Contemporary Publishing Inc., 12 Lakeside Park, Wakefield, MA (01880), 1978. 108 pages, $5.95 (softbound).

ANKYLOSING SPONDYLITIS—Discussions in Patient Management—Andrei Calin, MA, MRCP, MD, Assistant Professor of Medicine, Stanford University Medical Center; Chief of Rheumatology, Palo Alto Veterans Administration Hospital, Palo Alto, California; and James F. Fries, MD, Assistant Professor of Medicine, Stanford University Medical Center. Medical Examination Publishing Co. Inc., 969 Stewart Avenue, Garden City, NY (11530), 1978. 117 pages, $10.

ANNUAL REVIEW OF NEUROSCIENCE—Volume 1, 1978—Editor: W. Maxwell Cowan, Washington University School of Medicine, St. Louis; Associate Editors: Zach W. Hall, University of California School of Medicine; and Eric R. Kandel, College of Physicians and Surgeons of Columbia University, New York. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1978. 506 pages, $17.

ATLAS OF GRAY SCALE ULTRASONOGRAPHY—Kenneth J. W. Taylor, MD, PhD, Associate Professor, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1978. 411 pages, $35.

CLINICAL ASPECTS OF AGING—A Comprehensive Text prepared under the Direction of The American Geriatrics Society—Editor: William Reichel, MD, Chairman, Department of Family Practice, Franklin Square Hospital, Baltimore. The Williams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1978. 528 pages, $35.

CLINICAL PHARMACOLOGY—Basic Principles in Therapeulics—Second Edition—Edited by Kenneth L. Melmon, MD, Professor of Medicine and Pharmacology, and Chief, Division of Clinical Pharmacology; and Howard F. Morrelli, MD, Professor of Medicine and Pharmacology, and Vice Chairman (House Staff Affairs), Department of Medicine; University of California, San Francisco. Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1978. 1,146 pages, $25 (cloth); $19.95 (paperback).

COMMON-SENSE SUICIDE—The Final Right—Doris Portwood. Dodd, Mead & Company, 79 Madison Ave., New York City (10016), 1978. 142 pages, $6.95.

THE HUMAN PULMONARY CIRCULATION—Its Form and Function In Health and Disease—Second Edition—Peter Harris, MD, PhD, FRCP, Simon Marks Professor of Cardiology, Cardiothoracic Institute, University of London; Physician, National Heart Hospital; and Donald Heath, MD, PhD, FRCP, FRCPath, George Holt Professor of Pathology, University of Liverpool. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1977. 712 pages, $65.

MEALTIME MANUAL FOR PEOPLE WITH DISABILITIES AND THE AGING—Second Edition—Compiled by Judith Lannefeld Klinger, OTR, MA, with the Institute of Rehabiliation Medicine, New York University Medical Center, and Campbell Soup Company, Camden, NJ. Mealtime Manual, Box 38, Ronks, PA (17572), 1978. 269 pages, $3.25.

RECENT ADVANCES IN INTENSIVE THERAPY—Number One—Edited by I. McA. Ledingham, Reader in Surgery, University of Glasgow; Consultant Clinical Physiologist, Intensive Therapy Unit, Western Infirmary, Glasgow. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 257 pages, $23.

RECENT ADVANCES IN MEDICINE—Number Seventeen—Edited by D. N. Baron, MD, DSc, FRCP, FRCPath, Professor of Chemical Pathology, The Royal Free Hospital School of Medicine, London; Nigel Compston, MA, MD, FRCP, Physician, The Royal Free Hospital, Royal Masonic Hospital, and King Edward VII Hospital for Officers, London; and A. M. Dawson, MD, FRCP, Physician, St. Bartholomew's Hospital and King Edward VII Hospital for Officers, London, Physician to the Royal Household. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1977. 473 pages, $28.

SODIUM AND WATER HOMEOSTASIS—Volume I of CONTEMPORARY ISSUES IN NEPHROLOGY—Edited by Barry M. Brenner, MD, Samuel A. Levine Professor of Medicine, Harvard Medical School; Director, Laboratory of Kidney and Electrolyte Physiology, and Physician, Peter Bent Brigham Hospital, Boston; and Jay H. Stein, MD, Professor of Medicine and Director, Division of Renal Diseases, the University of Texas Health Science Center at San Antonio. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1978. 250 pages, $25.

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THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

August 12-13—**California Society of Anesthesiologists—Workshop.** Harrah's, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., San Mateo 94401.

September 8-9—**Update of Anesthetic Drugs and Monitoring.** STAN. Friday-Saturday.

October 7-8—**Practical Closed Circuit Anesthesia.** PMC. Saturday-Sunday. 12 hrs. $150.

CANCER

June 19-23—**Head and Neck Oncology.** UCLA. Monday-Friday.

June 29-30—**Oncology Conference.** USC at Disneyland Hotel, Anaheim. Thursday-Friday.

October 28-29—**Management of Cancer.** UCLA. Saturday-Sunday.

EMERGENCY MEDICINE

June 26-30—**Trauma—Major and Minor.** USC. Monday-Friday.

July 24-28—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $350.

August 7-11—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Islandia Hyatt House, San Diego. Monday-Friday. 40 hrs. $350.

September 11-15—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel, San Diego. Monday-Friday. 40 hrs. $350.

October 23-27—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

October 27-28—**Orthopedics for the Emergency Physician.** PMC. Friday-Saturday. 9 hrs. $150.

October 29-November 3—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Sunday-Friday. 40 hrs. $350.

MEDICINE

June 15-17—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 16-18—**Coronary Disease, Exercise Testing and Rehabilitation.** International Medical Education Corp. at Inn at the Park, Anaheim. Friday-Sunday. 13 hrs. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

June 21-22—**Practical Allergy and Immunology.** USC at Beverly Wilshire Hotel, Beverly Hills. Wednesday-Thursday. 15¼ hrs. $125.

June 23-24—**Bacterial, Viral and Fungal Infections of Importance in Clinical Practice.** Memorial Hospital Medical Center of Long Beach. Friday-Saturday. 10½ hrs. $100. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 24—**Allergy in Office Practice.** PMC Saturday. 6 hrs. $85.

June 29—**Renal Stones.** PMC. Thursday. 6 hrs. $85.

July 28-30—**Clinical Electrocardiography and Arrhythmia Management.** International Medical Education Corp. at Newporter Inn, Newport Beach. Friday-Sunday. 13 hrs. $195. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646.

August 5—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $295.

August 9-12—**Pediatric Dermatology.** STAN. Wednesday-Saturday. 24 hrs. $225; $75, residents. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101

August 16-19—**Medical Mycology-Dermatomycology—3rd Annual Postgraduate Course and Workshop.** UCI and Memorial Hospital Medical Center, Long Beach. Wednesday-Saturday. 33 hrs. $300. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

August 25-26—**Vascular Disease and the Brain.** Dominican Neurologic Institute and Dominican Santa Cruz Hospital. Friday-Saturday. 12 hrs. $150. Contact: Dominican Neurologic Institute, 1555 Soquel Dr., Santa Cruz 95065. (408) 476-0220, ext. 505.

August 25-27—**Dermatomycology.** UCSF. Friday-Sunday.

September 4-6—**"EEG, ABC"—13th Annual Course in Clinical Electroencephalography.** American Electroencephalographic Society at Hyatt Regency, San Francisco. Monday-Wednesday. Contact: American EEG Society Exec. Office, 38238 Glenn Ave., Willoughby, OH 44094. (216) 942-9267.

September 8-10—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton at Fishermans Wharf, San Francisco. Friday-Sunday. 13 hrs. $195. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

September 11-14—**EKG Self Assessment.** PMC and American College of Cardiology at Golden Gateway Holiday Inn, San Francisco. Monday-Thursday.

September 16-17—**Kidney Disease—18th Annual Scientific Symposium.** Kidney Foundation of Southern Calif. at Ambassador Hotel, Los Angeles. Saturday-Sunday. 8 hrs. $60. Contact: Mickie Hall Faris, KFSC, 1281 Westwood Blvd., Suite 200, Los Angeles 90024. (213) 473-6559.

September 17-21—**Pacific Dermatologic Association.** Hotel del Coronado, Coronado. Sunday-Thursday. 15½ hrs. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno NV 89509. (702) 323-2461.

September 28-30—**Clinical Immunology.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

September 29-October 1—**Cardiac Symptoms and Arrhythmias—Their Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $195. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

October 12-14—**Practical Cardiology—1978.** American College of Cardiology and UCSF at Del Monte Hyatt House, Monterey. Thursday-Saturday. Contact: Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 13-15—**Clinical Electrocardiography and Arrhythmia Management.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 15 hrs. $195. Contact: International Med. Ed. Corp., 64 Inverness Dr. East, Englewood, CO 80110. (800) 525-8646 toll free.

October 20-21—**Mycology Review.** STAN. Friday-Saturday. 16 hrs. $50; $20, residents. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 25-26—**46th Annual Fall Symposium and 11th Annual Griffith Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $65, member any Heart Assn.; $85, nonmember. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 27-28—**California Society of Internal Medicine—Annual Meeting.** Holiday Inn on Union Square, San Francisco. Friday-Saturday. Contact: CSIM, 703 Market St., 1412 Central Towers, San Francisco 94103. (415) 362-1548.

October 27-28—**Evaluation and Management of Allergic and Asthmatic Problems in Adults and Children.** UCD at Double Tree Inn, Monterey. Friday-Saturday.

OBSTETRICS AND GYNECOLOGY

August 26-September 1—**Practical Management of the Infertile Couple—2nd Annual Edward Tyler Symposium.** See Of Interest To All, August 26-September 1.

September 14-16—**Obstetrics and Gynecology—Annual Fall Symposium.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

(Continued on Page 32)

Tablets
Percodan® (II)

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg oxycodone terephthalate (WARNING May be habit forming), 224 mg. aspirin, 160 mg phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

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Manati, Puerto Rico 00701
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DUPONT

CONSIDERATIONS FOR ORAL NARCOTIC ANALGESIC USE:

1. Determine need

What is causing pain? How is it perceived by you and your patient?

2. Prescribe a rapid-acting agent

Select a readily-absorbed oral agent that usually acts within 15 to 30 minutes.

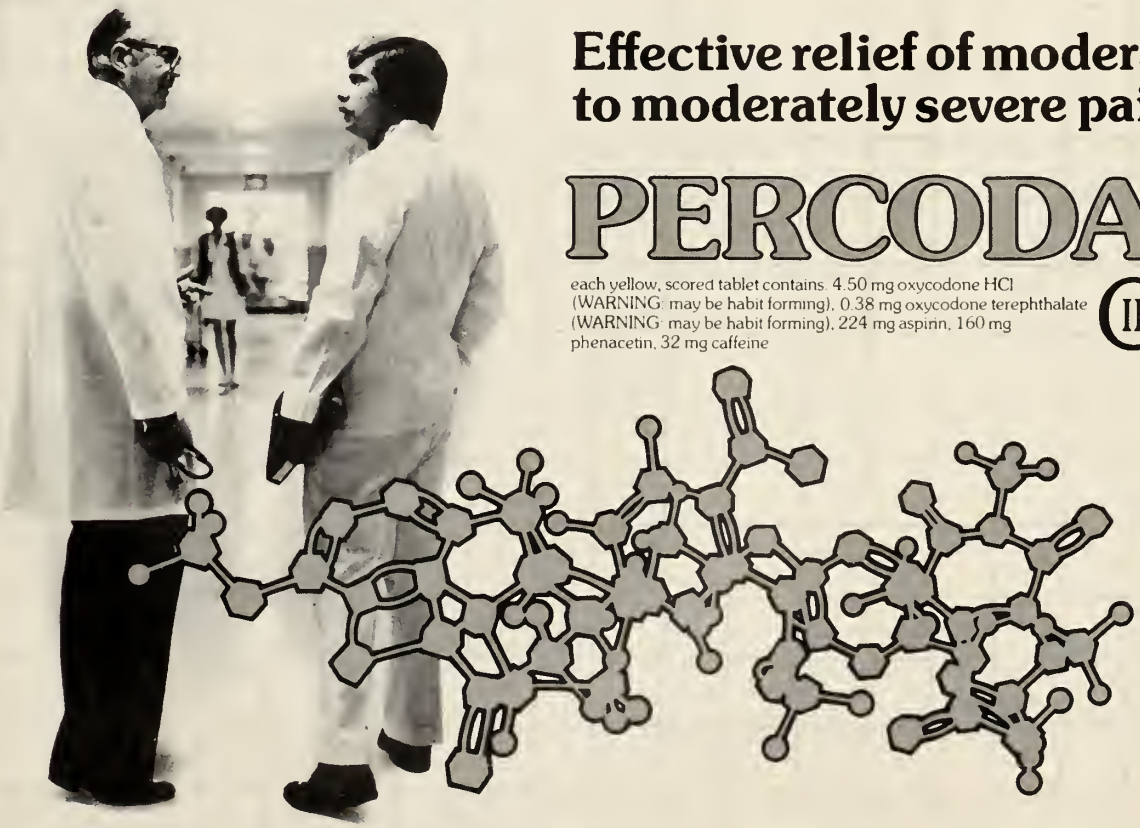
3. Minimize potential risk

Prescribe in limited quantities for selected patients.

Schedule II classification means no refills, no telephone Rx. Patients with persistent pain must return for your evaluation of analgesic needs.

4. Provide adequate analgesia with minimum doses

Consider PERCODAN® because patients rarely ask for increased dosage. PERCODAN® relief can last up to six hours–until time for next tablet.



Effective relief of moderate to moderately severe pain

Tablets

PERCODAN®

each yellow, scored tablet contains 4.50 mg oxycodone HCl (WARNING: may be habit forming), 0.38 mg oxycodone terephthalate (WARNING: may be habit forming), 224 mg aspirin, 160 mg phenacetin, 32 mg caffeine

CII

PERCODAN® is a registered trademark of Endo Inc.

Please see facing page for Brief Summary of prescribing information.

(Continued from Page 30)

September 17-23—**Advances in Obstetrics.** UCSF at Maui, Hawaii. One week.

September 21-22—**Progress in Perinatal Medicine.** Bay Area Chapter, National Foundation-March of Dimes; Kaiser-Permanente and UCSF at Hilton Hotel, San Francisco. Thursday-Friday. Contact: Arlene M. Mann, MD, Dir. of Public/Professional Ed., 1255 Post St., Suite 415, San Francisco 94109. (415) 441-1900.

September 29-30—**Office Gynecology Workshop.** PMC. Friday-Saturday. 9 hrs.

October 27—**Advances in Obstetrics and Gynecology.** No. Calif. Obstetrical and Gynecological Society at Red Lion Inn, Sacramento. Friday. 7 hrs. Contact: Solon Barbis, MD, 1816 Professional Dr., Sacramento 95825. (916) 482-6510.

PEDIATRICS

August 9-12—**Pediatric Dermatology.** See Medicine, August 9-12.

September 20-21—**Brennemann Memorial Lectures—35th Annual.** Los Angeles Pediatric Society at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Los Angeles Pediatric Society, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 21-22—**Progress in Perinatal Medicine.** See Obstetrics and Gynecology, September 21-22.

October 7-14—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center of Long Beach at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 22 hrs. $200. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 27-28—**Evaluation and Management of Allergic and Asthmatic Problems in Adults and Children.** See Medicine, October 27-28.

PSYCHIATRY

June 26-29—**Mental Research Institute Workshops.** Palo Alto. Monday-Thursday. Four workshops: (1) Brief Therapy; (2) Family Crisis: Intervention Strategies; (3) Working with the Victims of Sexual Assault and Violent Crimes; (4) Introduction to Hypnotherapy, Theory and Practice. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

June 26-30—**Comparative Psychotherapies.** USC. Monday-Friday.

June 30-July 1—**Human Problems: Ordinary and Extraordinary—3rd Don D. Jackson Memorial Conference.** Mental Research Institute at Sir Francis Drake Hotel, San Francisco. Friday-Saturday. Contact: Peggy Smith, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

July 8—**Community Treatment of Schizophrenia.** Mental Research Institute, Palo Alto. Saturday. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

July 10-13—**Practical Aspects of Family Therapy.** Mental Research Institute, Palo Alto. Monday-Thursday. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

September 4-6—**"EEG, ABC"—13th Annual Course in Clinical Electroencephalography.** See Medicine, September 4-6.

October 25-29—**American Academy of Child Psychiatry—25th Annual Meeting.** Hotel del Coronado, Coronado. Wednesday-Sunday. Contact: Virginia Q. Bausch, Exec. Dir., AACP, Suite 201A, 1424 16th St., NW, Washington, DC 20036. (202) 462-3754.

RADIOLOGY AND PATHOLOGY

June 27-30—**Society of Nuclear Medicine—25th Annual Meeting.** Anaheim. 21 hrs. $40, members; $60, nonmembers. Contact: Margaret Glos, Exec. Dir., SNM, 475 Park Ave. S., N. Y., NY 10016. (212) 889-0717.

July 30-August 5—**Ultrasound and Computed Tomography.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Saturday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

August 16-19—**Medical Mycology-Dermatomycology—3rd Annual Postgraduate Course and Workshop.** See Medicine, August 16-19.

August 25-27—**Dermatomycology.** See Medicine, August 25-27.

September 9—**Gastrointestinal Radiology.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Saturday. 7 hrs. $30. Contact: Shirley Gach, Education and Research Dept., SCPMG, 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4241.

October 14-22—**International Body Imaging Conference—3rd Annual.** West Park Hospital at Maui, Hawaii. 9 days. 25 hrs. $295. Contact: Ronald J. Friedman, MD, West Park Hospital, Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 19-23—**American Institute of Ultrasound in Medicine—24th Annual Meeting.** Town and Country Hotel, San Diego. Thursday-Monday. 40 hrs. Contact: Tyra Kite, Meeting Coordinator, 6161 N. May Ave., Suite 260, Oklahoma City, OK 73112. (405) 840-3723.

October 20-21—**Mycology Review.** See Medicine, October 20-21.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

June 15-17—**Hip Course.** UCLA. Thursday-Saturday.

June 15-17—**Highlights of Ophthalmology.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday. 16 hrs. $195.

June 15-17—**Retina Workshop.** St. Mary's Hospital and Medical Center at Silverado Country Club, Napa. Thursday-Saturday. 12 hrs. $95. Contact: Med. Staff Secretary, St. Mary's Hosp. and Med. Ctr, 450 Stanyan St., San Francisco 94117.

June 29—**Renal Stones.** See Medicine, June 29.

August 4-5—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

September 4-6—**"EEG, ABC"—13th Annual Course in Clinical Electroencephalography.** See Medicine, September 4-6.

September 22-23—**Ophthalmology Update VII.** PMC and Update Foundation at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $225.

September 22-23—**Laparoscopy for Hepatology and General Surgery.** Cedars-Sinai Medical Center, Los Angeles. Friday-Saturday. Contact: Lore Kahane, Room 2049, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

October 6-7—**Intraocular Lens Implantation Course.** Santa Monica Hospital. Friday-Saturday. $600; $300, residents. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

October 12-13—**Eye Enucleation.** UCSF. Thursday-Friday.

October 28-29—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 30-November 10—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Dir., Temporal Surgical Dissection Course, ERI, 256 S. Lake St., Los Angeles 90057.

OF INTEREST TO ALL PHYSICIANS

June 16-18—**San Diego Chapter, California Academy of Family Physicians—22nd Annual Postgraduate Symposium.** Town and Country Hotel, San Diego. Friday-Sunday. 15 hrs. Contact: Don Wilson, MD, 233 A St., Suite 1005, San Diego 92101.

June 17—**Gerontological Seminar—3rd Annual.** UCSF at Diablo Valley College, Rossmoor. Saturday. 7 hrs. $50.

June 17-18—**Practical Applications of Biofeedback in the Health Sciences—5th Annual Seminar.** UCLA at Marriott Hotel, Los Angeles Airport. Saturday-Sunday. 12½ hrs. $185.

June 18-24—**Family Practice Refresher Course—9th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. Sunday-Saturday.

June 20—**Hypertension—Rationale for Appropriate Work-Up and Advances in Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

June 23-24—**Sexual Abuse: Issues for Health Practitioners.** UCSF at Sheraton Palace, San Francisco. Friday-Saturday. $80. Contact: UCSF, Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

June 30-July 1—**Human Problems: Ordinary and Extraordinary.** See Psychiatry, June 30-July 1.

July 5-August 2—**Introduction to Integral Medicine.** UCLA. Wednesday evenings. 12½ hrs. $120.

July 10-21—**Intensive Workshop in Sex Therapy Skills.** UCSF Human Sexuality Program. Two weeks. $400. Contact: Human Sexuality Program, 350 Parnassus, No. 700, San Francisco 94143. (415) 666-4787.

July 17-21—**Family Practice Refresher Course.** UCLA at Century Plaza Hotel, Los Angeles. Monday-Friday. 42½ hrs. $300.

July 22-25—**Allergy and Clinical Immunology for Non-Allergist Physicians.** American Assn. for Clinical Immunology and Allergy at Newporter Inn, Newport Beach. Saturday-Tuesday. 26 hrs. $260. Contact: AACIA, P.O. Box 912, Omaha, NE 68101. (402) 551-0801.

July 31-August 11—**Intensive Workshop in Sex Therapy Skills.** See above, July 10-21.

August 11-16—**Management of Pain.** PMC and Academy of Pain Research at Hyatt Regency, San Francisco. Friday-Wednesday. 30 hrs. $275.

August 12-23—**Annual Postgraduate Refresher Course.** USC at Hawaii. 12 days.

August 13-18—**Family Practice Refresher Course—6th Annual.** UCD at Del Monte Hyatt House, Monterey. Saturday-Thursday. 30 hrs. $225.

August 26-September 1—**Practical Management of the Infertile Couple—2nd Annual Edward Tyler Symposium.** Tyler Medical Clinic and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. 17 hrs. $150. Contact: Exclusive Travel, Inc., 3345 Wilshire Blvd., Los Angeles 90010.

September 16-17—**National Amphetamine Conference.** Amphetamine Evaluation and Physician Training Project, UCSF, Calif. Soc. for the Treatment of Alcoholism and Other Drug Dependencies, Haight-Ashbury Free Med. Clinic and CMA at UCSF. Saturday-Sunday. 11 hrs. $30. both days; $20. one day. Contact: Amphetamine Evaluation and Physician Training Project, 409 Clayton St., San Francisco 94117. (415) 626-6763.

September 23—**Drug Abuse.** UCLA. Saturday.

September 25-28—**American Academy of Family Physicians—Annual Scientific Assembly.** Brooks Hall, San Francisco. Monday-Thursday. Contact: AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

September 30-October 1—**Eight Common Clinical Problems for the Primary Care Physician.** UCLA. Saturday-Sunday.

October 2-6—**Primary Care.** STAN. Monday-Friday. 27 hrs. $290.

October 15-19—**International Health Society, Inc.—31st Annual Scientific Assembly.** Los Angeles. Sunday-Thursday. 24 hrs. Contact: James P. Pappas, MD, MPH, Exec. Dir., IHS, 7316 River Hill Rd., Oxon Hill, MD 20021. (301) 839-9361.

October 22-26—**Autogenic Training.** UCLA at Yosemite. Sunday-Thursday.

October 30-November 3—**Intensive Care.** STAN. Monday-Friday. 25½ hrs. $290.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

Health Research Group of the American Institutes for Research. A not-for-profit research corp. CME research project seeks physician input. Physicians in general or family practice in non-urban areas of Calif. may be contacted to participate in a major research project on development of a continuing medical education system for doctors in office practice. Project will offer, without charge, up to 30 hrs. Category I credit in return for trying out and critiquing a newly developed set of instructional materials. These materials, entitled "Management of Adult Asthma: for General and Family Physicians," and the delivery system to be tried out were developed by the Health Research Group of the American Institutes for Research under contract to the National Heart, Lung, and Blood Insitute/National Institutes of Health. Contact: Muriel H. Bagshaw, MD, Project Dir., Health Research Group, American Institutes for Research, P.O. Box 1113, Palo Alto 94302. (415) 493-3550.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470.

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

ALLERGY

October 12-14—**West Coast Society of Allergy and Immunology 17th Annual Scientific Session.** Jantzen Beach Thunderbird, Portland. Contact: Sondra Gleason, 5210 SW Corbett Ave, Portland 97201.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

May 31-June 3—**Oregon Society of Internal Medicine and Oregon Chapter, American College of Physicians Annual Meeting.** Salishan Lodge, Gleneden Beach. Contact: Joyce Gullixson, Oregon Society of Internal Medicine, 5210 SW Corbett Avenue, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

July 12-14—**Woodland Park Hospital Summer Symposium on Drug Dilemmas.** Thunderbird Motor Inn, Astoria. Contact: R. Thomas Gustafson, MD, 10300 NE Hancock Street, Portland 97220

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

June 26-27—**Inflammatory Bowel Disease—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, June 26, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, June 27, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

July 20-22—**Cardiology Symposium: American College of Chest Physicians—Pacific Northwest Chapter.** Thursday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

August 17-18—**Difficult Problems in Pediatric Orthopaedics.** Thursday-Friday. Washington Plaza Hotel, Seattle. 14 hrs. Fee: $150. Contact: Dept. of Orthopaedics, ZC-10, Childrens Orthopedic Hospital and Medical Center, P.O. Box C5371, Seattle, WA 98105. (206) 634-5250.

Index to The Western Journal of Medicine Advertising

American College of Chest Physicians
Postgraduate Course: "Pulmonary Medicine" ... 14

Audio-Digest Foundation ... 7

Beth Israel Hospital
Aspen Mushroom Conference ... 25

Bristol Laboratories
Tegopen ... 14, 15

Classified ... 24, 25, 26

Eli Lilly and Company
Darvocet-N 100 ... 11

Endo Laboratories
Percodan ... 30, 31

Geigy Pharmaceuticals
Brethine ... 8, 9, 10

Hewlett Packard ... 5

Mead Johnson Laboratories
Colace & Vasodilan ... 19, 20

Physicians & Surgeons Insurance Exchange ... 12

Presto Foods Inc.
Mocha Mix ... 16

Roche Laboratories
Dalmane ... 22, 23
Librax ... 2nd Cover, 1, 2
Librium ... 17, 18
Valium ... 3rd & 4th Cover

San Jose State University
Summer Gerontology Institute ... 28

Smith Kline & French Company
Dyazide ... 13

University Microfilms International ... 27

The Upjohn Company
Tolinase ... 6

Warren-Teed Pharmaceuticals Inc.
Kaon Elixir ... 3

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